INDEX NUMBER

American Academy of Allergy, Tenth Annual Meeting, Shamrock Hotel, Houston, Texas, February 1, 2, 3, 1954.

The Journal of Allergy

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Official Organ of AMERICAN ACADEMY OF ALLERGY

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UNIVERSITY OF MICHIGAN
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MEDICAL

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1. Dill, J. L.: Postgrad. Med. 4:413, 1948.

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Vol. 24, No. 6, November, 1953. The Journal of Allergy is published Bi-Monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $8.50; in Canada and other foreign countries, $9.00. Entered as Second-Class Matter, November 15, 1929, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

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The Journal of Allergy

VOL. 24 NOVEMBER, 1953 No. 6

Original Articles

EGG WHITE EDEMA IN RATS AND ADRENAL ACTIVITY

H. VAN CAUWENBERGE, M.D., J. LECOMTE, M.D., J. GOBLET,* AND M. VLIERS, PH.D., LIÈGE, BELGIUM

INTRAPERITONEAL injection of egg white in rats induces edema of the paws, nose, and tongue, hemoconcentration and hypotension. The mechanism of this reaction is not yet well known. It could conceivably be caused by a local release of histamine or histamine-like substance. Adrenalectomy sensitizes to this edema and leads to death in a certain percentage of animals.[1, 2, 4] In similar conditions, adrenocortical extract prevents death but does not inhibit edema. Many workers have tried to inhibit the egg white edema syndrome by various pharmacologic substances or by stress such as exercise, cold, and formalin injection.[2, 7, 8, 9] Since epinephrine protects against egg white edema in the normal rat, Clark and Mackay think that "alarming stimuli" may act by releasing endogenous epinephrine.[3]

We have, in this article, studied the effect of intraperitoneal egg white injection on adrenal cholesterol and ascorbic acid as well as upon the circulating eosinophils.

METHODS

Our experiments were carried out on 69 adult male rats weighing from 125 to 200 grams fed on a standard diet and kept at constant temperature. These animals from two different rearings were divided into two groups corresponding to each rearing.

In the first group, 15 acted as controls and were not injected, 30 rats received an intraperitoneal injection of 1 ml. of egg white associated with 0.5 ml. of a chlorazol blue sky solution.

In the second group, 12 animals acted as controls and 12 others received an injection of fresh egg white and blue.

All the animals were sacrificed three or four hours after the injection. The degree of edema was estimates

+	Scrotum colored in blue.
++	Edema of the paws.
+++	Important edema of the paws and nose colored in blue.
++++	Important edema of the paws and important blue coloration.
0	No edema.

From the Department of Internal Medicine and Chemical Research in the University of Liège, Belgium.

Received for publication April 6, 1953.

*Medical student.

The amounts of ascorbic acid and of cholesterol in the adrenals, the number of circulating eosinophils were studied in each rat.

Ascorbic acid was extracted from the adrenals with metaphosphoric acid and titrated against a solution of 2 to 6 dichlorophenol-indophenol.

TABLE I

		EDEMA	ASCOBIC ACID 100% = 356 μG./100 MG. OF GLAND		CHOLESTEROL 100% = 2.934 μG./100 MG. OF GLAND		EOSINOPHILS 100% = 93/ CU. MM.	
			Per Cent		*Per Cent*		*Per Cent*	
Controls intact animals	1	-	96		76		76	
	2	-	108		104		108	
	3	-	100		108		72	
	4	-	82		112		86	
	5	-	112	$\sigma = 11\%$	124	$\sigma = 16\%$	130	$\sigma = 23\%$
	6	-	117		76		140	
	7	-	98		72		65	
	8	-	80		98		80	
	9	-	89		96		100	
	10	-	120		104		104	
	11	-	100		126		122	
	12	-	92		84		72	
	13	-	102		102		120	
	14	-	97		112		100	
	15	-	107		106		125	
Animals injected with egg white and blue	1	+++	69		130		80	
	2	+++±	70		146		120	
	3	+++	79		149		93	
	4	-	79		165		93	
	5	++++	83		116		83	
	6	+++	125		141		70	
	7	+++±	63	M = 70%	116	M = 104%	65	M = 80%
	8	+++	85		80		72	
	9	++++	81		70		77	
	10	+++	53		153		76	
	11	+++	68		144		89	
	12	++	67		78		55	
	13	+++	50		109		95	
	14	+++	69		93		106	
	15	++++	74		77		92	
	16	++++	67		75		64	
	17	++++	67		84		68	
	18	+++	60		93		72	
	19	+++	71		100		50	
	20	++++	68		87		75	
	21	+++	80		93		88	
	22	++++	54		79		77	
	23	++	59		77		94	
	24	+++	59		87		61	
	25	+++	71		83		94	
	26	++++	79		100		72	
	27	++	50		112		77	
	28	++++	79		72		77	
	29	++	53		122		83	
	30	++++	73		95		77	

Total cholesterol was estimated by photometry after its extraction from crushed adrenal tissue with ethyl alcohol followed by Liebermann's reaction.

The circulating eosinophils were counted on blood drawn from the rat's heart when it was killed. The counts were made by the direct eosin method using Dunger's fluid. The blood was withdrawn in three white-cell pipettes and

six counts were made on each specimen of blood in four double-celled Fuchs-Rosenthal counting chambers.

RESULTS

Our results are summarized in Tables I and II.

After the intraperitoneal injection of egg white and blue, a significant fall of adrenal ascorbic acid is observed in the two groups of animals we studied. No change occurs in the adrenal cholesterol or in the circulating eosinophils.

There is no relation between the degree of edema and the value of the fall of adrenal ascorbic acid.

TABLE II

		EDEMA	ASCORBIC ACID 100% = 413 μG./100 MG. OF GLAND		CHOLESTEROL 100% = 2.66 μG./100 MG. OF GLAND		EOSINOPHILS 100% = 112 CU. MM.	
			Per Cent		*Per Cent*		*Per Cent*	
Controls intact animals	1	-	107		89		75	
	2	-	104		72		110	
	3	-	88		94		122	
	4	-	79		108		125	
	5	-	121		122		76	
	6	-	88	$\sigma = 12\%$	102	$\sigma = 17\%$	79	$\sigma = 19\%$
	7	-	97		79		94	
	8	-	108		86		122	
	9	-	96		120		126	
	10	-	109		92		89	
	11	-	92		122		85	
	12	-	111		114		97	
Animal	1	++	58		106		74	
	2	++	72		118		74	
	3	++++	67		94		79	
	4	++	70		95		80	
	5	+++	42		145		65	
	6	++	-	$M = 68\%$	67	$M = 94\%$	83	$M = 82\%$
	7	++	86		120		74	
	8	+++	50		63		108	
	9	++	75		85		91	
	10	++++	84		77		98	
	11	+++	78		83		79	
	12	++	62		74		79	

DISCUSSION

A fall of adrenal ascorbic acid occurs after the intraperitoneal injection of egg white but no significant modification of adrenal cholesterol or of circulating eosinophils is observed. How is this to be explained?

A similar fact has already been reported by us in a previous article.[10] We have indeed observed in rats after intraperitoneal injection of mercaptoethylamine (or cysteinamine or 1573 L. Labaz), 10 mg. per 100 grams of body weight, a fall of more than 50 per cent of adrenal ascorbic acid. No changes occur in adrenal cholesterol nor in circulating eosinophils.

Nelson has already shown that the modifications of the circulating eosinophils after administration of cortisone or compound F are directly correlated with changes in the plasmatic levels of 17-hydroxycorticosteroids. Compound S or its acetate does not produce these hematologic modifications.[6] On the basis of this experimentation it may be thought that neither egg white asso-

ciated with blue sky solution nor cysteinamine liberates 17-hydroxycorticosteroids. In these conditions is another group of adrenal hormones liberated by the adrenals?

A fall of circulating eosinophils, of adrenal ascorbic acid and cholesterol is regularly to be observed with sufficient doses of ACTH or salicylates. If the amount of corticotropic hormone (unpublished) or sodium salicylates[11] injected is progressively reduced, the initial significant fall of circulating eosinophils disappears but the significant ascorbic acid and cholesterol decrease remains; when smaller doses of the drugs are injected, the latter also disappear. In that experimentation with ACTH or salicylate a decrease of more than 30 per cent of ascorbic acid is regularly accompanied by a significant change in the circulating eosinophils. That is not observed in our study here reported. Thus we are led to conclude that no corticotropic hormone is liberated by cysteinamine or egg white injection.

Only hypophysectomy would enable us to eliminate the intervention of a pituitary-adrenal stimulation and to relate the observed fall of ascorbic acid to a metabolic process independent of adrenal hyperactivity.

SUMMARY AND CONCLUSIONS

Edema occurs in rats after egg white intraperitoneal injection and is accompanied by an important decrease of adrenal ascorbic acid. No significant change of adrenal cholesterol nor circulating eosinophils is observed. The modifications of ascorbic acid do not seem related to a liberation of 17-hydroxycorticosteroids by the adrenals or of ACTH by the pituitary gland. However, an adrenocorticotropic stimulation cannot be eliminated.

This phenomenon has an important bearing upon the use of adrenal ascorbic acid depletion in the researches on the activity of the pituitary-adrenal cortex axis.

We are indebted to the Belgian National Foundation for Scientific Research for a grant-in-aid of this investigation.

REFERENCES

1. Halpern, B. N., and Briot, M.: Étude pathogénique et thérapeutique du syndrome oedémateux provoqué chez la rat par l'ovalbumine, Arch. internat. pharmacodyn. **82:** 247, 1950.
2. Clark, W. G., and MacKay, E. M.: Effect of l-Epinephrine and l-Arterenol on Egg White Edema in the Rat, Proc. Soc. Exper. Biol. & Med. **71:** 86, 1949.
3. Clark, W. G., and MacKay, E. M.: Effect of Epinephrine, Antihistaminics and Adrenergic Blockade on Egg White Edema in Adrenal Insufficient Rats, Proc. Soc. Exper. Biol. & Med. **72:** 510, 1949.
4. Leger, J., and Masson, G.: Effect of Antihistaminic Substances on the Edema Produced by Egg White in the Rat, Am. J. M. Sc. **214:** 305, 1947.
5. Leger, J., and Masson, G. M. C.: Studies on Egg White Sensitivity in the Rat. Influence of the Endocrine Glands, Ann. Allergy **6:** 131, 1948.
6. Nelson, Don H., Sandberg, Avery A., Palmer, J. G., and Tyler, F. H.: J. Clin. Investigation **31:** 843, 1952.
7. Selye, H.: Studies on Adaptation, Endocrinology **21:** 169, 1937.
8. Selye, H.: Stress, Montreal, Canada, 1950, Acta Inc.
9. Selye, H.: Annual Report on Stress, Montreal, Canada, 1951, Acta Inc.
10. Van Cauwenberge, H., Roskam, J., Heusghem, C., Fischer, P., Deltour, G., and Bacq, Z. M.: Action de la mercaptoéthylamine sur la teneur en acide ascorbique des glandes surrénales du rat, Arch. Int. Physiol. **61:** 124, 1953.
11. Van Cauwenberge, H., and Betz, H.: Salicylates and Neuro-endocrine Stimulation, Lancet **262:** 1083, 1952.

THE CHEMISTRY OF ALLERGENS. XII. PROTEOLYSIS OF THE COTTONSEED ALLERGEN

JOSEPH R. SPIES, PH.D., DORRIS C. CHAMBERS, M.S., E. J. COULSON, PH.D., HARRY S. BERNTON, M.D., AND HENRY STEVENS, PH.D., WASHINGTON, D. C.

THE isolation and properties of the principal allergen of cottonseed, CS-1A, have been described in a series of articles from this laboratory starting in 1939. CS-1A was immunologically distinct from other allergens and antigens in cottonseed and was classified as a natural proteose. The protein nature of CS-1A was established by chemical properties and isolation procedures,[1-3] amino acid composition,[4, 5] and antigenic properties.[6-10] The present study was undertaken to answer several questions concerning the effect of digestive proteolytic enzymes on the cottonseed allergen as well as to obtain general fundamental information on this subject. The questions were: (1) is allergenic activity due to structural peculiarities which make the allergen resistant to proteolysis; (2) can partial enzymic hydrolysis take place without loss of allergenic properties; (3) is allergenic activity due to an unrecognized nonprotein contaminant present in trace proportions.

The role of proteolysis in the body's defense against ingested allergenic proteins and the immunologic significance of protein hydrolytic products have been subjects of much investigation and speculation. Complete review of the literature on this subject is outside the scope of this article, only a few references particularly pertinent to the present problem being cited.

Opinion of Zinsser and Bayne-Jones[11] and of Hartley,[12] based on their evaluation of then existing evidence, was that the antigenic property of native proteins is destroyed early on hydrolysis, probably before formation of such relatively high-molecular-weight, cleavage products as proteoses. Landsteiner[13] stated that amino acids and low-molecular weight peptides are inactive as antigens and that attempts to produce antibodies for relatively high-molecular weight proteoses have been, in general, unsuccessful. However, instances of anaphylaxis and formation of antibodies for peptic heteroproteins absorbed on charcoal have been reported.[13] Loss of capacity to react with precipitins for unaltered protein by peptic digests has been observed.[13]

Ratner and Gruehl[14] and Walzer[15] reviewed the earlier history of the immunologic aspects of the absorption of ingested proteins. They considered the positive passive transfer reactions obtained on ingestion of allergens to be caused by absorption of unaltered allergenic proteins.

Stull and Hampton[16] determined the antigenicity of primary and secondary proteoses prepared by peptic digestion of proteins from several sources using the Schultz-Dale technique. New specificities were developed in some cases

From the Allergen Research Division, Bureau of Agricultural and Industrial Chemistry, United States Department of Agriculture, Washington 25, D. C.
Presented in part before the ninth meeting of the American Academy of Allergy, February, 1953, Boston, Mass.
Received for publication June 29, 1953.

and in other cases the products were not antigenic. The degrees of antigenicity and whether or not new specificities developed depended on the source of the protein and the experimental technique employed.

Urbach and associates[17, 18] studied the immunologic behavior of the propeptans, which are the degradation products obtained by peptic digestion of foods with subsequent mild tryptic digestion. Urbach[19] stated that pollen propeptans stripped of all native protein still possessed ability to react in passively sensitized sites.

Much difficulty in this field is caued by the indefinite nature of protein hydrolytic products, the possible presence of immunologically significant traces of undigested, native protein in enzyme digests, the use of complex foods or pollens as substrates, the lack of determination of the degree of enzyme digestion, and other difficultly controlled factors. Availability of the principal allergen of cottonseed as a well-defined protein fraction, CS-1A, prompted this study.

The present article is a progress report describing results of proteolysis of CS-13-Endo, a purified fraction of CS-1A. The crystalline enzymes used were trypsin, chymotrypsin, pepsin, and carboxypeptidase.

EXPERIMENTAL

CS-1A.—Fraction CS-1A was isolated from depigmented, defatted cottonseed as previosuly described.[1, 2, 5]

Preparation of Substrate, CS-13-Endo.—An unimportant polysaccharide and some denatured protein were eliminated from CS-1A by precipitation of the active fraction with picric acid and recovery of the fraction, CS-13, by removal of the picric acid. CS-13 is separable into fractions by dialysis. The smaller molecules in CS-13 which pass through the membrane possess the same antigenic specificity as the larger molecules retained by the membrane.[20] Therefore, the fraction remaining inside the membrane, after prolonged dialysis of CS-13, CS-13-Endo, is an ideal substrate because any increase in dialyzability after proteolysis of CS-13-Endo can be used as a measure of proteolysis and also dialysis can be used to fractionate the enzyme hydrolysates. Details of the preparation of the substrate, CS-13-Endo, from CS-1A are described below.

One hundred grams of CS-1A (ash- and water-free basis) was dissolved in 1,900 ml. of water, and 2,080 ml. of a saturated solution of picric acid was added with stirring. The viscous suspension was cooled to 2 to 3° C. overnight. The suspension was centrifuged in the batch bowl of the Sharples supercentrifuge at 45,000 r.p.m. for twenty minutes. The clear supernatant solution was discarded. The picrate was washed by dispersing in 400 ml. of water followed by supercentrifuging. For removal of picric acid the dried picrate (82.7 grams) was suspended in 4,000 ml. of water, and 15 grams of sodium bicarbonate was added slowly with vigorous stirring. The pH of the solution was 7.0. The pH was adjusted to 9.0 with dilute sodium hydroxide, and 4,000 ml. of cold absolute ethanol was added. The pH of the clear solution was adjusted immediately to 6.0 with 50 per cent acetic acid. To the resulting suspension was

added 12,300 ml. of ethanol. The suspension was kept at 5° C. for four days. The supernatant solution was siphoned off and discarded. The solid was washed successively with 1,500 ml. and 400 ml. portions of cold ethanol. The solid was stirred mechanically with 2,000 ml. of water until dispersed or dissolved. The insoluble matter was removed by centrifugation and discarded. To the solution was added 100 ml. of 1N sodium acetate, buffered at pH 5.6, and 8,400 ml. of ethanol. The resulting suspension was cooled and the pH adjusted to 6.0-6.2 with acetic acid. After standing at 5° C. overnight the slightly cloudy supernatant solution was separated and discarded. The solid was washed successively with 1,000 ml. and 400 ml. portions of cold ethanol. The solid was dissolved in 750 ml. of water and the solution was clarified by centrifugation. The clear solution was filtered into 3,000 ml. of cold ethanol. The heavy suspension was cooled and flocculated by adding dilute acetic acid until the pH was 6.0-6.2. After standing at 5° C. for two days the precipitate was separated by centrifuging at 5° C. The dried precipitate (41.1 grams) was dissolved in 700 ml. of water and the solution was clarified by centrifugation. The solution was filtered into 2,800 ml. of cold ethanol and the suspension was flocculated by adjustment of the pH to 6.0-6.2 with acetic acid and sodium hydroxide; 35 ml. of 1N sodium acetate buffer, pH 5.6, also being added. The solid, separated from the cold suspension by centrifugation, was washed once with 1,000 ml. of cold ethanol and dried in a vacuum over calcium chloride. The solid, designated CS-13, was ground to pass a 40 mesh sieve and equilibrated with air. The yield was 34.7 grams. CS-13 contained 18.83 per cent nitrogen and 4.0 per cent carbohydrate (ash- and water-free basis).

For dialysis, a solution containing 33.2 grams of CS-13 in 330 ml. of water was placed inside a leak-tested, Visking cellulose casing. Toluene was used as preservative. The casing was suspended in a 4 l. beaker with the knotted ends of the casing hanging over the edge of the breaker. The solution was dialyzed against 1,000 ml. portions of water. To the clarified dialysate and endo solutions were added 0.1 volumes of 1N sodium acetate buffer, pH 5.6. The solutions were poured into four volumes of cold ethanol, and if flocculation did not occur, it was induced by adjustment of the pH to 6.0-6.2 with 50 per cent acetic acid and sodium hydroxide solution. The suspensions were stored at 5° C. overnight and the precipitates isolated by centrifugation. The solids were washed once with ethanol and dried in vacuum over calcium chloride. Yields and analyses of the fractions are shown in Table I. Six dialysate fractions were obtained which accounted for 50.2 per cent of the starting CS-13. The dialyzed residue, CS-13-Endo, weighed 9.7 grams or 29.2 per cent of the CS-13. CS-13-Endo contained 17.8 per cent nitrogen and 7.7 per cent carbohydrate (ash- and water-free basis).

Enzymes.—The enzyme preparations were obtained from Worthington Biochemical Laboratory. Pepsin was twice crystallized from alcohol. Trypsin was "salt free," twice crystallized. Carboxypeptidase was a thrice crystallized water suspension. The Worthington chymotrypsin was recrystallized four times by E. F. Jansen, Western Regional Research Laboratory.

TABLE I. DIALYSIS OF COTTONSEED ALLERGEN, CS-13

FRACTION	TIME OF DIALYSIS DAYS	NITROGEN IN DIALYSATE % OF TOTAL	YIELD OF SOLID* GRAM	YIELD OF SOLID % OF TOTAL	ANALYSIS OF FRACTION	
					NITROGEN† %	CARBOHYDRATE‡ %
Dialysate No. 1	7	10.5	2.5	7.5	19.6	0.75
Dialysate No. 2	14	12.1	3.4	10.2	19.5	0.85
Dialysate No. 3	21	12.1	3.4	10.2	19.5	0.87
Dialysate No. 4	20	9.5	2.8	8.4	19.8	0.85
Dialysate No. 5	28	9.1	2.4	7.2	19.3	0.86
Dialysate No. 6	42	8.8	2.3	6.7	19.5	0.86
CS-13-Endo	132§	——	9.7	29.2	17.8	7.70

*Air-dried basis.
†Ash- and water-free basis.
‡Determined by the method described in Ref. 30.
§Total time of dialysis.

Proteolysis.—The substrate was a solution containing 50 mg./ml. of CS-13-Endo. The solvent for the trypsin-chymotrypsin and the chymotrypsin-trypsin proteolysis was 0.2M boric acid-potassium chloride buffer, pH 8.5; the pH of the substrate solution being 8.33. The solvent for carboxypeptidase digestion was 0.2M phosphate buffer, pH 7.4; the pH of the substrate solution being 7.27. For digestion with pepsin, the pH of a water solution of CS-13-Endo was adjusted to 1.73 with 6N hydrochloric acid. After thirty hours' digestion with pepsin the pH was 2.10. The pH was readjusted to 1.79 with hydrochloric acid. The pH was 1.8 at the end of digestion. Toluene was used as preservative.

Proteolysis was carried out at 35° ± 0.1 C. The proportion of enzyme to CS-13-Endo was 1 to 50, a second equal amount of enzyme being added after forty-eight hours. Following forty-eight hours' treatment with trypsin and also with chymotrypsin the solutions were halved. To one half was added a second quantity of the starting enzyme and to the other half was added, appropriately, either trypsin or chymotrypsin. Aliquots of each substrate solution were removed before the first addition of enzyme to serve as controls. Control solutions were kept at 35° during the corresponding proteolysis.

Measurement of Proteolysis.—The recently described ultraviolet spectrophotometric method for analysis of amino acids and peptides with their copper salts[21] was used to determine the rate and time of completion of proteolysis. Analyses were run on 5 ml. aliquots of solution prepared by diluting 0.25 ml. of substrate solution into 50 or 100 ml. of water.

Comparative Rates of Dialysis.—Five milliliters of solution was placed in an 8-inch length of leak-tested, 18/32 inch Visking sausage casing. The dialyzing tubing was suspended in 100 ml. of water in a 250 ml. beaker by fastening the tied ends of the casing over the edge of the beaker. Toluene was used as preservative. After twenty-four hours, without agitation, the outer solution was removed and nitrogen content was determined by the Kjeldahl micromethod. From the nitrogen content of the solution and its volume the percentage of nitrogen dialyzed in twenty-four hours was determined. Results are shown in Table II.

Cutaneous Tests.—A scratch which just penetrated the epidermis was made on the inner forearm of a Type II[1] cottonseed-sensitive subject. The test solu-

tion was placed on the scratch and worked in with a clean toothpick. The intensity of the reaction was determined by the size of the wheal produced in fifteen or thirty minutes. Simultaneous control tests were conducted to provide a comparison of potency.

TABLE II. SUMMARY OF THE EFFECT OF ENZYMES ON COTTONSEED ALLERGIC FRACTION, CS-13-ENDO

ENZYME OR ENZYME COMBINATION	TIME OF ACTION HR.	COPPER-REACTING NITROGEN % OF TOTAL	NITROGEN DIALYZED IN 24 HR. % OF TOTAL	CUTANEOUS TEST*	
				1:50,000	1:500,000
Trypsin	71	23.8	40.2	0	±
Trypsin-Chymotrypsin†	48-24	25.0	50.6	0	0
Control	71	6.3	0.8	4+	3+
Chymotrypsin	72	19.7	39.1 ± 0.0§	2+	±
Chymotrypsin-trypsin‡	48-24	27.7	56.5 ± 0.0§	0	0
Control	72	6.2	0.7	4+	3+
Pepsin	72	11.9	28.2 ± 0.2§		3+
Control‖	72	6.0	10.3 ± 0.2§		3+
Carboxypeptidase	72	10.3	19.8		2+
Carboxypeptidase	240	12.7	23.1 ± 0.1§		4+
Control	72	7.2			4+
Control	240	6.3	3.6		3+

*Diluted on a nitrogen basis.

†Trypsin forty-eight hours followed by chymotrypsin for twenty-four hours.

‡Chymotrypsin forty-eight hours followed by trypsin for twenty-four hours.

§Average of duplicate determinations.

‖The relatively high percentage of nitrogen dialyzed from this control solution is undoubtedly due to dialysis from the strongly acid solution used for peptic digestion. In a different experiment in which the acid control solution was neutralized before dialysis, the per cent nitrogen dialyzed was almost the same as that which dialyzed from a similar solution which had never been acidified.

RESULTS AND DISCUSSION

The relative rates and amounts of proteolysis of CS-13-Endo by trypsin, chymotrypsin, pepsin, and carboxypeptidase are shown in Fig. 1. The percentage of copper-reacting nitrogen in enzyme hydrolysates and control solutions is plotted as ordinates against time in days as abscissas. Enzymic hydrolysis is proportional to the percentage of copper-reacting nitrogen in the hydrolysates. The percentage copper-reacting nitrogen divided by 0.54 gives an approximate percentage-degree of completion of hydrolysis. This factor is based on the amino acid composition of CS-1A fractionation products.[22]

Results, summarized in Table II, show the percentages of copper-reacting nitrogen, the dialyzability, and the skin-reactivity of the final enzyme hydrolysates compard to control solutions.

CS-13-Endo was digested by all four enzymes. Of the enzymes used alone, trypsin caused the most rapid and complete hydrolysis in seventy-two hours (curve T); the copper-reacting nitrogen was 23.8 per cent and the nitrogen dialyzed in twenty-four hours was 40.2 per cent. Digestion with trypsin for forty-eight hours followed by digestion with chymotrypsin for twenty-four hours or digestion in reverse order with these enzymes caused more hydrolysis than did hydrolysis for seventy-two hours with either enzyme used alone (curves *T-Ch* and *Ch-T*). The most hydrolysis was caused by digestion with chymotrypsin for forty-eight hours followed by digestion with trypsin for

twenty-four hours. After this treatment the copper-reacting nitrogen was 27.8 per cent and the nitrogen dialyzed was 56.5 per cent as compared to 25 per cent copper-reacting nitrogen and 50.6 per cent nitrogen dialyzed when the digestion was carried out in reverse order.

Skin-reacting capacity of CS-13-Endo was destroyed by digestion with trypsin but slight activity remained after chymotrypsin digestion. The skin-reacting capacity of CS-13-Endo was destroyed by the combined action of trypsin and chymotrypsin regardless of the order of their use. These results unequivocally confirm the conclusions from previous work that allergenic activity of CS-1A is caused by protein and not by an unrecognized nonprotein contaminant.

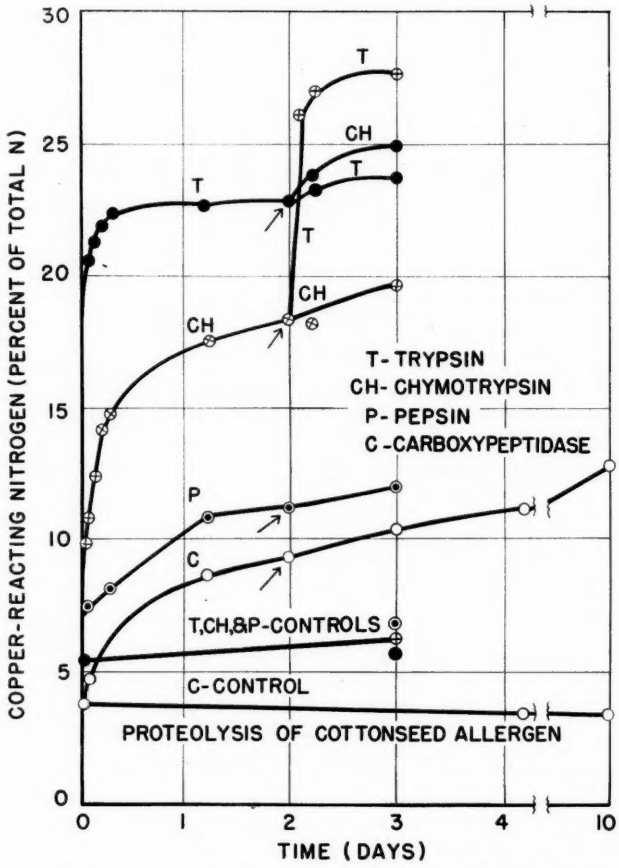

Fig. 1.—Relative rates and amounts of proteolysis of CS-13-Endo.

Both pepsin and carboxypeptidase hydrolyzed CS-13-Endo to a lesser degree than did trypsin or chymotrypsin. The skin-reacting capacity was not destroyed nor apparently even diminished by either pepsin or carboxypeptidase. A peptic digest was fractionated by dialysis. Fast- and slow-dialyzing fractions were obtained. The slow-dialyzing fraction was more skin-reactive than the fraction remaining inside the dialyzing membrane. This indicated

that the intact protein is not necessary for allergenic activity but that peptide bonds may be split by pepsin without destroying allergenic activity. However, this point must be investigated further before an unequivocal conclusion can be reached.

In contrast, on dialysis of the carboxypeptidase digest, the fraction remaining inside the membrane was more skin-reactive than the fractions which dialyzed. This is to be expected because in general carboxypeptidase splits amino acids from the ends of polypeptide chains whereas pepsin splits peptide bonds deeper within the peptide chain.

The precipitinogenic capacities of the enzyme digests of CS-13-Endo were determined with the agar plate method of Ouchterlony,[23, 24] using rabbit antiserum from rabbits sensitized to CS-1A. Solutions containing 0.1 mg. of nitrogen per milliliter were used for precipitin tests. Trypsin, chymotrypsin, and carboxypeptidase caused a decrease in the precipitinogenic capacity of the allergen but did not destroy it completely. Pepsin completely destroyed precipitinogenic capacity* as shown by the agar plate method, but the peptic digest gave a slightly positive precipitin reaction by the ring test. Reason for this discrepancy is not known. These results indicated the complexity of enzymic action in relation to precipitinogenic and skin-reactive properties of substrates and conditions of the experiment. It should be pointed out, as did Stull and Hampton,[16] that varying experimental conditions or substrate preparations may give varying results because of the large number of possible split products that can result from substances as complex as proteins. Further fundamental studies along these lines are needed.

The peptic digest of CS-13-Endo was antigenic as shown by its capacity to sensitize guinea pigs. The peptic digest retained 25 per cent of its capacity to induce contraction in sensitized guinea pig uteri as shown by the Schultz-Dale technique. No new specificity was detected in the peptic digest as shown by cross-neutralization tests with CS-13-Endo using Schultz-Dale tests.

The observation that a skin-reactivity is retained by a dialyzable fragment of the pepsin digest of CS-13-Endo is of possible significance in relation to the absorption of ingested allergens. Freeman,[25] Lewis and Grant,[26] and, independently, M. Walzer[27, 28] first observed that ingested egg and fish allergens were absorbed into the circulatory system and were capable of inciting passive transfer reactions in sensitized sites. It has been generally regarded that specific reaction of allergen in sensitized sites was a property of the unaltered allergen. The possibility was suggested by Spies, Chambers, Bernton, and Stevens[29] that digestive enzymes might cause alteration of the cottonseed allergen without destroying its specific property of reacting with reagins. Positive passive transfer reactions were obtained with a fraction of the peptic digest of CS-13-Endo which had passed through a dialyzing membrane. But compari-

*The precipitinogenic capacities of a peptic digest of CS-13-Endo and of CS-13-Endo were determined using the method of Ouchterlony as follows: The pH of each solution was adjusted to 6.9. Rabbit antiserum was prepared using CS-1A as antigen. Twofold serial dilutions were used in each series of tests. CS-13-Endo gave precipitin reaction in dilutions from 0.1 to 0.0007 mg./ml. of nitrogen. The peptic digest gave no precipitin reaction in dilutions from 3.2 to 0.0015 mg./ml. of nitrogen.

son of the passive transfer potency* of this fraction with that of CS-13-Endo was not sufficiently precise to eliminate conclusively the possibility that the reaction obtained with the dialyzable fraction was not due to some unchanged allergen in the peptic digest. That skin-reactivity is retained by a dialyzable fraction of the peptic digest supports the view that more highly diffusible, active fragments of allergen are produced in the stomach by pepsin or pepsin and gastric acidity in the first stages of digestion than existed in the original allergen. This may contribute to increasing the speed of absorption as shown by the rapidity with which passively sensitized sites are incited to reaction when allergen is ingested. It should be pointed out, however, that undialyzed CS-1A contains some allergen which is readily dialyzable. CS-13-Endo was used as substrate for the present studies to eliminate, as far as possible, this dialyzable portion of CS-1A.

SUMMARY

The effects of four crystalline enzymes were studied on CS-13-Endo, a purified fraction of CS-1A, the principal allergen of cottonseed. The enzymes were trypsin, chymotrypsin, pepsin, and carboxypeptidase. CS-13-Endo was digested by all of these enzymes. Skin-reacting capacity was destroyed by trypsin. Decreased activity remained after digestion with chymotrypsin. These results unequivocally show that allergenic activity is caused by protein and not by an unrecognized nonprotein contaminant in CS-13-Endo. Both pepsin and carboxypeptidase digested CS-13-Endo but to a lesser degree than did trypsin or chymotrypsin. The skin-reacting capacity was not destroyed by pepsin or carboxypeptidase. A dialyzable fraction of the pepsin digest was slightly more potent in skin-reactivity than the nondialyzable fraction. This indicated that the intact protein was not essential for allergenic activity. The peptic digest of CS-13-Endo was antigenic. No new specificity developed in the peptic digest.

REFERENCES

1. Spies, J. R., Bernton, H. S., and Stevens, H.: The Chemistry of Allergens. I. Isolation of an Active Fraction From Cottonseed, J. ALLERGY **10**: 113, 1939.
2. Spies, J. R., Coulson, E. J., Bernton, H. S., and Stevens, H.: The Chemistry of Allergens. II. Isolation and Properties of an Active Protein Component of Cottonseed, J. Am. Chem. Soc. **62**: 1420, 1940.
3. Spies, J. R., and Umberger, E. J.: The Chemistry of Allergens. VI. Chemical Composition and Properties of an Active Carbohydrate-Free Protein From Cottonseed, J. Am. Chem. Soc. **64**: 1889, 1942.
4. Spies, J. R.: The Chemistry of Allergens. V. The Amino Acid Content of Active Protein and Polysaccharidic Protein Fractions From Cottonseed, J. Am. Chem. Soc. **63**: 2994, 1941.
5. Spies, J. R., Coulson, E. J., Chambers, D. C., Bernton, H. S., Stevens, H., and Shimp, J. H.: The Chemistry of Allergens. XI. Properties and Composition of Natural Proteoses Isolated From Oilseeds and Nuts by the CS-1A Procedure, J. Am. Chem. Soc. **73**: 3995, 1951.

*The threshold quantities of a fraction of the peptic digest of CS-13-Endo that had passed through a membrane and of CS-13-Endo required to produce positive passive transfer reactions were determined. Three sites were sensitized on each upper arm of the recipient using 0.05 ml. of serum from a cottonseed-sensitive subject in each site. Three days later equal quantities of nitrogen of the dialysis fraction and of CS-13-Endo were introduced into corresponding sites on opposite arms. The wheals which formed were measured after fifteen to thirty minutes. The threshold quantities of nitrogen required to produce positive reactions were from 1 to 10 $\eta\mu g$ for each fraction. In the three recipients tested, CS-13-Endo appeared slightly more potent than the peptic digest dialysate but the latter fraction produced wheals with pseudopods and heat in the same concentrations of nitrogen as did CS-13-Endo.

6. Coulson, E. J., Spies, J. R., and Stevens, H.: The Immunochemistry of Allergens. I. Anaphylactogenic Properties of a Proteic Component of Cottonseed, J. Immunol. **41**: 375, 1941.
7. Coulson, E. J., Spies, J. R., and Stevens, H.: The Immunochemistry of Allergens. II. Antigenic Studies by the Dale Method of the Electrophoretic Fractionation Products of the Protein-Carbohydrate Fraction, CS-1A, From Cottonseed, J. Immunol. **46**: 347, 1943.
8. Coulson, E. J., and Spies, J. R.: The Immunochemistry of Allergens. III. Anaphylactogenic Potency of the Electrophoretic Fractionation Products of CS-1A From Cottonseed, J. Immunol. **46**: 367, 1943.
9. Coulson, E. J., and Spies, J. R.: The Immunochemistry of Allergens. IV. Effect of Dilute Acid on Anaphylactogenic Activity, Specificity, and Reagin-Neutralization Capacity of Cottonseed Allergenic Fractions, J. Immunol. **46**: 377, 1943.
10. Coulson, E. J., Spies, J. R., and Stevens, H.: The Immunochemistry of Allergens. V. Comparison of the Rates of Dialysis of Crystalline Ovalbumin and the Cottonseed Allergen, CS-1A, J. Immunol. **47**: 443, 1943.
11. Zinsser, H., and Bayne-Jones, S.: Textbook of Bacteriology, ed. 8, New York, London, 1939, D. Appleton-Century Company, Inc.
12. Hartley, P.: A System of Bacteriology, London, 1931, His Majesty's Stationery Office, vol. 6, p. 231.
13. Landsteiner, K.: The Specificity of Serological Reactions, revised edition, Cambridge, Mass., 1945, Harvard University Press, pp. 45-46.
14. Ratner, B., and Gruehl, H. L.: Passage of Native Proteins Through the Normal Gastro-Intestinal Wall, J. Clin. Investigation **13**: 517, 1934.
15. Walzer, M.: A Critical Review of Some Recent Developments in the Field of Allergy, J. ALLERGY **7**: 597, 1936.
16. Stull, A., and Hampton, S.: A Study of the Antigenicity of Proteoses, J. Immunol. **41**: 143, 1941.
17. Urbach, E., Jaggard, G., and Crisman, D. W.: Experimental Approach to Oral Treatment of Food Allergy. II. Immunologic Properties of Food Propeptans, Ann. Allergy **3**: 172, 1945.
18. Urbach, E., and Gottlieb, P. M.: Allergy, New York, 1943, Grune & Stratton, Inc.
19. Urbach, E.: The Chemical and Immunologic Basis of Oral Pollen Propeptan Therapy in Hay Fever, Ann. Allergy **5**: 147, 1947.
20. Coulson, E. J., Spies, J. R., and Stevens, H.: The Immunochemistry of Allergens. IX. The Relationship of Carbohydrate to the Antigenic Properties of the Allergenic Protein From Cottonseed, J. Immunol. **62**: 171, 1949.
21. Spies, J. R.: An Ultraviolet Spectrophotometric Micromethod for Studying Protein Hydrolysis, J. Biol. Chem. **195**: 65, 1952.
22. Spies, J. R., and Chambers, Dorris C.: Spectrophotometric Analysis of Amino Acids and Peptides With Their Copper Salts, J. Biol. Chem. **191**: 787, 1951.
23. Ouchterlony, Ö.: An In-Vitro Test of the Toxin-Producing Capacity of Corynebacterium Diphtheriae, Lancet **256**: 346, 1949.
24. Bjorklund, B.: Specific Inhibition of Precipitation as an Aid in Antigen Analysis With Gel Diffusion Method, Proc. Soc. Exper. Biol. & Med. **79**: 319, 325, 1952.
25. Freeman, J.: Discussion on Paroxysmal Rhinorrhoea, Proc. Roy. Soc. Med. (section on laryngology) **18**: 29, 1925.
26. Lewis, T., and Grant, R. T.: Vascular Reactions of the Skin to Injury. VII. Notes on the Anaphylactic Skin Reaction, Heart **13**: 219, 1926.
27. Walzer, M.: A Direct Method of Demonstrating the Absorption of Incompletely Digested Proteins in Normal Human Beings, J. Immunol. **11**: 249, 1926.
28. Walzer, M.: Studies in Absorption of Undigested Proteins in Human Beings. I. A Simple Direct Method of Studying the Absorption of Undigested Protein, J. Immunol. **14**: 143, 1927.
29. Spies, J. R., Chambers, Dorris C., Bernton, H. S., and Stevens, H.: Quantitative Estimation of the Absorption of an Ingested Allergen, J. ALLERGY **16**: 267, 1945.
30. Heidelberger, M., and Kendall, F. E.: Carbohydrate-Containing Proteins of the Hemolytic Streptococcus, J. Immunol. **30**: 267, 1936.

SIGNIFICANCE OF CHANGES IN THE EXPIRATORY RATE OBSERVED DURING MEASUREMENT OF THE VITAL CAPACITY IN ASTHMA

FRANCIS C. LOWELL, M.D., AND IRVING W. SCHILLER, M.D., BOSTON, MASS.

PROLONGED expiration is a well-known feature of bronchial asthma and emphysema and it is readily demonstrated and measured with kymographic tracings obtained during performance of the vital capacity or by a timing device. The value of the vital capacity has been thereby greatly increased. Changes in the speed of expiration as well as the vital capacity were observed in the studies on the induction of asthmatic attacks with inhaled aerosols of allergenic extracts.[1] Furthermore, among patients with pulmonary disease, the volume expired in the first second during the performance of the vital capacity has been shown to correlate well with the maximum breathing capacity.[2]

This report is a presentation and discussion of some of the features of the expiratory tracing obtained in normal and asthmatic subjects during the performance of the vital capacity.

METHODS

Vital capacities were done in the usual manner. The patient was instructed to make a maximal inspiration and then to expire with maximal effort into a mouthpiece and tube (¾ inch internal diameter) leading to a metal or plastic[3] water-type spirometer, the bell of which was attached by a thread or wire to a pen which recorded expiration on paper moved by a kymograph. For normal subjects the paper was moved at a speed of 3.66 cm. per second but for patients with asthma or emphysema, the speed was usually reduced to 0.56 cm. per second. The expiratory tracing obtained was a smooth curve. Varying effort during expiration, cough, or attempts to obtain additional air caused irregularities in the curve readily detected by inspection. Occasionally, oscillations of the water in the spirometer also caused irregularities. Administration of aerosols was carried out as described elsewhere.[1]

RESULTS

Fig. 1 illustrates the changes which took place in a patient with severe bronchial asthma who was treated over a period of eight days with cortisone by mouth. Each expiratory tracing shown was the greatest vital capacity and the most rapid expiratory rate selected from a number of attempts both before and after the administration of six inhalations of an aerosol of isopropylarterenol 1:200 from a nebulizer. After receiving 300 mg. of cortisone

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

Received for publication June 26, 1953.

by mouth in the first twenty-four hours, the greatest of several vital capacities was 2,750 c.c. Upon receiving six inhalations of aerosol, the vital capacity rose to 3,220 c.c. Upon repeating the procedure the following day (total dose of cortisone, 500 mg.) the vital capacity was 2,900 c.c., rising to 3,970 c.c. after six inhalations of aerosol. Similar but more marked changes followed the administration of aerosol the third day (total dose of cortisone, 700 mg.).

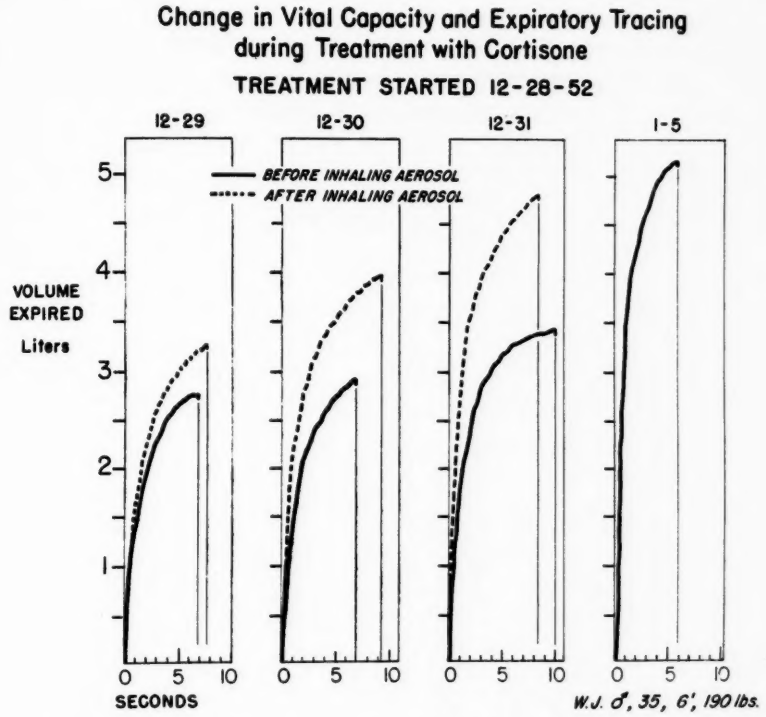

Fig. 1.—Tracings made during measurement of the vital capacity before and after inhalation of isopropylarterenol in a patient under treatment with cortisone.

Finally, after eight days of treatment (total dose of cortisone, 1,450 mg.), the vital capacity rose to 5,200 c.c., a normal value. During the first three days of treatment and during a period when the vital capacity was increasing, the total time required for the expiration of air either increased or remained approximately the same, but decreased at the end of eight days of treatment even though the vital capacity was much greater. The volume of air expired within the first second increased markedly from the third to the eighth day of treatment. The per cent of the vital capacity expired in the first second changed little in the first two days of treatment, ranging from 40 per cent to 50 per cent whether aerosol was given or not. On the third day there was a marked increase in this figure and, on the eighth day, 71 per cent of the total volume was expired in the first second.

Fig. 1 also shows an increasing effect of isopropylarterenol on the vital capacity during the first three days of treatment. This indicates that the

degree of response to a drug may depend on the clinical status of the patient as well as on the effectiveness of the drug used, an important point in assessing the value of drugs by means of the vital capacity.

Fig. 2 shows an expiratory tracing produced by a normal male with the paper moving approximately six times as fast as in Fig. 1. The vital capacity was 4,600 c.c. and the total time required to expire this volume was slightly under three seconds. The volume expired in the first second was 3,350 c.c. and the per cent expired in the first second was 72.8. The slope of a tangent drawn at any point on the curve will represent the speed of expiration at that instant. As can be readily seen, the speed of expiration, initially rapid, decreased throughout the expiratory effort.

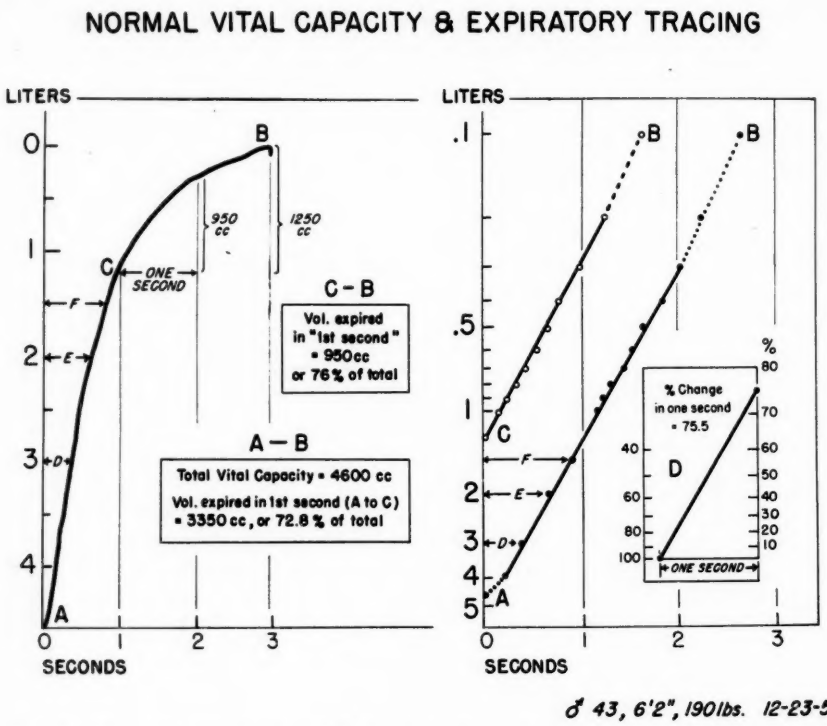

Fig. 2.—The cut (D) in the right-hand portion of the figure illustrates how the per cent change in the rate of expiration may be determined graphically. The logarithmic scale on the left is the same as that of the ordinate of the semilogarithmic plot of the expiratory tracing *A-B*. Here, however, the cycle begins at 100. The scale on the right is obtained by subtracting the smaller numbers of the left-hand scale from 100.

When, as shown by the graph in the right-hand portion of Fig. 2, the expiratory curve is plotted on graph paper with the time along the abscissa and the logarithm of the volume (expressed as that remaining to be expired) along the ordinate, the slope of the straight line obtained represents the rate of change in the speed of expiration. This can also be expressed as the per cent change per second in the speed of expiration, a figure which may be found by drawing a parallel to the straight line *A-B* starting from a point representing some multiple of 10 on the logarithmic scale (Fig. 2, *D*). It is

convenient to number this scale so that the per cent change may be read directly. The point where this parallel intersects a vertical line representing the elapse of one second gives the per cent change within this period of time. In this instance it is 75.5 per cent, slightly larger than the earlier figure found by measurement of the volume expired in the first second. The difference between the two figures is caused chiefly by inertia of the apparatus and air mass as expiration begins.*

The line obtained by plotting the expiratory curve on semilogarithmic paper (Fig. 2) deviates from a straight line at both ends. At the beginning (*A*), this occurs because the maximum rate of expiration is not obtained at once because of inertia. The break in the line near the end of expiration may represent a real change in the manner in which air leaves the lung but may also be explained in part by the selection of the end of expiration as one coordinate. This may be incorrect for the curve with which we are dealing but will be disregarded for present purposes.

Consideration of the plot of the expiratory tracing on semilogarithmic paper leads to the recognition of a further characteristic of the expiratory tracing, namely, that the rate of change in the speed of expiration is a measurement which is entirely independent of the vital capacity. This can be shown by treating that portion of the expiratory curve between *B* and *C*, representing 1,300 c.c., in a manner similar to that between *A* and *C*. The volume expired in the first second after *B* is 950 c.c., or 76 per cent of the total between *B* and *C*. Here the factor of inertia is again negligible as the apparatus is already in motion and indeed is slowing down, and therefore the figure is larger than that derived from the volume expired in the second immediately following the beginning of expiration.

Were inertia of the apparatus and air mass eliminated and were all expiratory tracings similar to that shown in Fig. 2, the per cent expired in the first second and the per cent change per second in the expiratory speed would be identical. Furthermore, it would appear possible to derive this value from a generous segment of an expiratory curve. Neither a maximal inspiration nor a complete expiration, as done in the performance of a vital capacity, would be necessary. However, as will be shown, the expiratory tracing obtained from some patients with chronic pulmonary disease differs markedly with respect to the change in the speed of expiration from that shown in Fig. 2.

Fig. 3 shows the result of plotting the expiratory curves from Fig. 1 with semilogarithmic coordinates. Relatively straight lines were obtained from each of the three pairs and the last curve. Upon the administration of aerosol, however, the rate of change in the speed of expiration was significantly decreased in each instance after expiration had proceeded for one and one-half seconds or more. Although slow rates of change in the speed of expiration have been characteristic of the patients with chronic pulmonary

*In certain instances, inertia has operated, again early in expiration, to distort the tracing in the other direction as well, by causing the rapidly moving bell temporarily to rise beyond a point representing the volume of air actually expired.

emphysema that we have studied, this decrease after the administration of a bronchodilator should not in itself be regarded as a measure of the patient's disability because the vital capacity is indeed larger as is also the absolute speed of air flow.

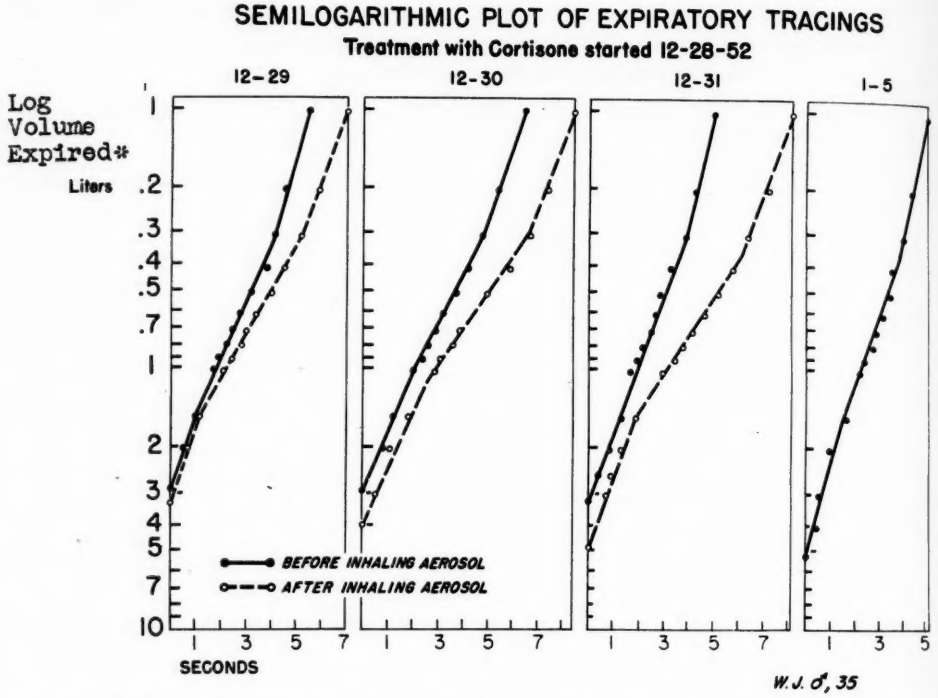

Fig. 3.—Tracings shown in Fig. 1 plotted on semilogarithmic coordinates. Tracings shown in Fig. 3 plotted on semilogarithmic coordinates in the same manner as the tracing shown in Fig. 2.

The changes in the expiratory tracing which took place in the course of an induced asthmatic attack are shown in Fig. 4. The subject, S. F., was a 58-year-old white man who, sometime previously, had suffered a severe constitutional reaction with asthma and hives, occurring shortly after an intramuscular injection of procaine penicillin.[4] Tracing A was obtained at a time when he felt well and was symptom-free. Tracing B was obtained a few minutes later, after two inhalations of an aerosolized solution of penicillin G containing 10,000 units per milliliter. Tracing C was obtained a few minutes after five inhalations of aerosolized isopropylarterenol 1:200 had been given to relieve the mild induced asthmatic attack. It is clear that inhalation of penicillin caused a reduction in vital capacity and a slowing of the expiratory rate, and that inhalation of the second aerosol caused a return of the vital capacity to the previous level and an increase in the speed of expiration. The rather striking difference between expiratory tracings A and C, readily apparent on inspection of the two curves, cannot be appreciated by mere measurement of the totals or the volumes expired in the first second.

The plot of curve A and B on semilogarithmic paper (Fig. 4) reveals that the change in the speed of expiration, though almost the same for the

two curves, was not constant throughout. After the expiration of 1,500 c.c. to 2,000 c.c. the rate of change decreased from approximately 45 per cent to approximately 20 per cent where it remained over a period of six seconds. However, after the administration of isopropylarterenol by aerosol, the rate of change was not only greater but was almost constant throughout expiration.

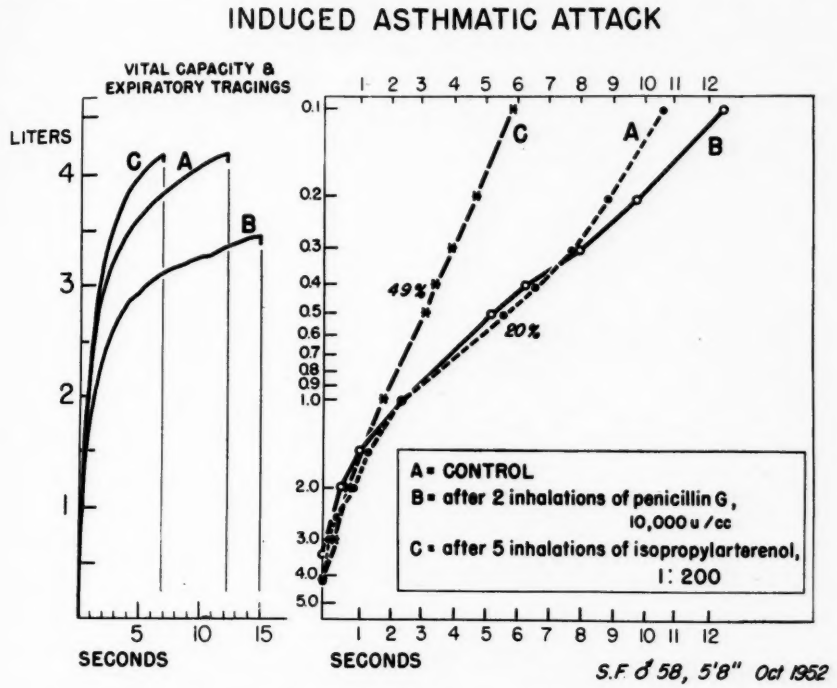

Fig. 4.—*Left,* Tracings made during measurement of the vital capacity before inhalation of an aerosol of penicillin (*A*), afterward (*B*), and then following inhalation of isopropylarterenol (*C*). *Right,* The same tracings plotted on semilogarithmic coordinates.

That the rate of change in the speed of expiration did not remain constant in curves A and B (Fig. 4) during the first two seconds of expiration suggests that air was leaving some portions of the lung in a manner different from other portions, or that the lung was not homogeneous. One might infer, therefore, that in this instance the asthma was, to some degree at least, patchy in distribution. After inhalation of isopropylarterenol the "asthmatic patches" may have changed in a manner to conform with the rest of the lung. At the present time the significance of these changes must remain a matter for speculation. These findings strongly indicate, however, that in the interpretation of the vital capacity a complete expiratory tracing will give more information than any single measurement or index.

SUMMARY

Spirographic tracings obtained during the performance of vital capacities are discussed from the point of view of a number of artifacts and the possible significance of the manner in which the speed of expiration changes. The

rate of this change may be determined by plotting time on the abscissa and the logarithm of the volume remaining to be expired along the ordinate.

Analysis of the curves obtained indicates:

1. During forced expiration air leaves the normal lung with a speed which changes (i.e., slows) at a constant or almost constant rate.

2. The rate of change in the speed of expiration may vary during a single expiratory effort among patients with chronic lung disease depending on poorly understood intrapulmonary factors.

3. In some patients with pulmonary disease, no single measurement or index derived from the so-called timed vital capacity can be regarded as truly representing the manner in which air is expired from the lungs. However, this is readily recognized with a kymographic tracing made with the paper moving at the rate of 0.5 cm. per second or more.

REFERENCES

1. Lowell, F. C., and Schiller, I. W.: Measurement of Changes in Vital Capacity as a Means of Detecting Pulmonary Reactions to Inhaled Aerosolized Allergenic Extracts in Asthmatic Subjects, J. ALLERGY **19**: 100, 1948.
2. Gaensler, E. A.: Analysis of the Ventilatory Defect by Timed Vital Capacity Measurements, Am. Rev. Tuberc. **64**: 256, 1951.
3. Lowell, F. C., Schiller, I. W., and Lowell, A.: The Use of a Closed System in the Study of Asthma and Emphysema, J. ALLERGY **23**: 335, 1952.
4. Boger, W. P., Sherman, W. B., Schiller, I. W., Siegal, S., and Rose, B. (Edited by Irving W. Schiller): Allergic Reactions to Penicillin, J. ALLERGY **24**: 383, 1953.

CHANGE IN THE RATE OF OXYGEN SATURATION OF THE ARTERIAL BLOOD ASSOCIATED WITH INDUCED ASTHMATIC ATTACKS

FRANCIS C. LOWELL, M.D., IRVING W. SCHILLER, M.D., MARY T. LYNCH, M.D., AND ALICE LOWELL, M.D., BOSTON, MASS.

THE following report describes attempts to determine how rapidly the arterial oxygen saturation rises upon inhalation of 100 per cent oxygen in asthmatic subjects experiencing varying degrees of asthma and having been purposely rendered hypoxic. The speed of this rise might provide an indication of pulmonary efficiency. The procedure used was an adaptation of one described by Fowler and Comroe[1] and again by Douglas and Edholm.[2] More recently a similar technique has been applied to the study of patients with pulmonary disease.[3]

Two patients, both asthmatic, were selected for study because of the ease with which asthmatic attacks could be produced in them and because they were familiar with the procedure.

METHODS

With a noseclip in place, the subject breathed from a low-resistance valve assembly,* drawing gas from a meteorologic balloon of large capacity enclosed in an airtight 50-gallon drum. The expired gas passed through a recording spirometer to enter the space between the wall of the balloon and that of the drum. Thus the subject breathed from an enclosed space from which the expired gas could not mix with that which he breathed and which, except for the spirometer, was rigid. A second drum identical with the first was coupled to it and 3-way valves so arranged as to permit abrupt change from one gas reservoir to another without disturbing the patient or interrupting the respiratory tracing. Changes in the oxygen saturation of the arterial blood were measured with a 2-channel CMR Millikan oximeter, the same earpiece being used throughout. The apparatus, the adjustment of the oximeter, and the arrangement for administering aerosols have been described elsewhere.[4] In the present study a continuous record of the oxygen saturation was obtained with a manually operated pointer, connected by a fine wire to a pen similar to that recording respiration, which was made to follow the light spot on the saturation scale of the galvanometer.†

An experiment was carried out as follows. With the earpiece in place and after the ear thickness readings had become stable, the subject breathed 100 per cent oxygen from one of the gas reservoirs for ten minutes, whereupon the light spot of the galvanometer was set at 100 per cent on the scale. After breathing air from the room for a few minutes, the subject breathed 10 per

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

Received for publication, May 21, 1953.

*Warren E. Collins Inc., 2-way plastic J valve.

†Rubicon Co., Cat. No. 3418.

cent oxygen from the other reservoir until the saturation fell to 85 per cent. At this point valves were turned so that the subject again breathed 100 per cent oxygen and continued to do so until the saturation reading showed no further change. The expiratory reserve volume, the inspiratory capacity, and the vital capacity were determined in the usual manner.

The two subjects, both of whom were described briefly elsewhere,[5] had severe asthma with marked improvement under treatment with cortisone and both had evidence of pulmonary emphysema, of moderate degree in R. G. (Patient No. 10[5]) and of marked degree in R. D. (Patient No. 4[5]). Detailed information on R.D. is available in another report.[6]

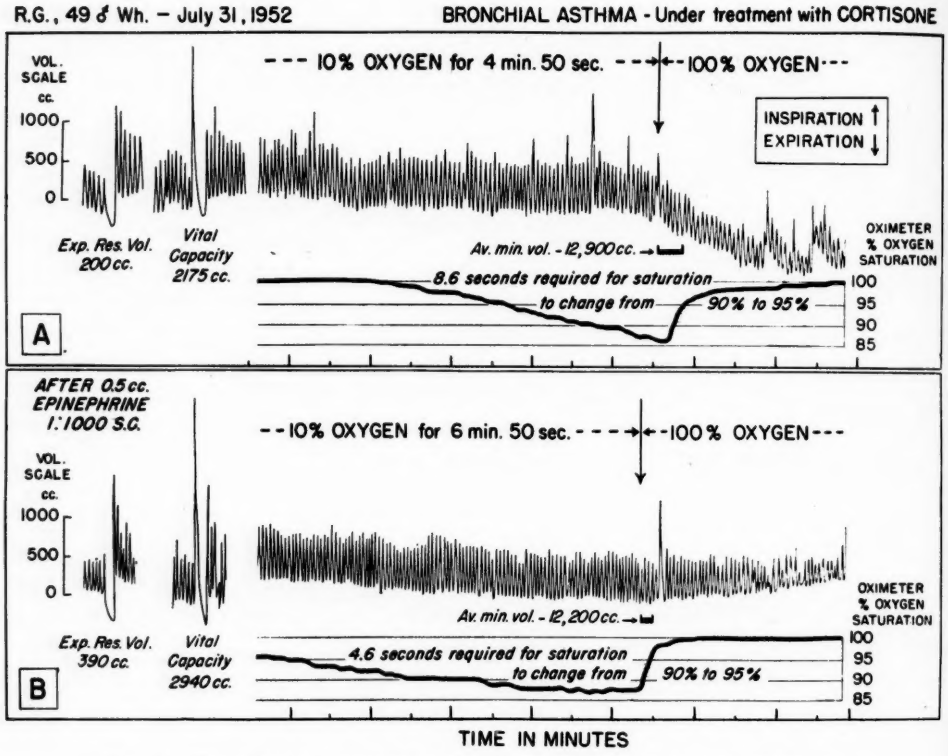

Fig. 1.—The effect of epinephrine on the rate of rise in oxygen saturation.

RESULTS

Fig. 1 shows the results of two tests done on R.G. Before the procedure was started the patient stated that he was almost free of asthma. After the expiratory reserve volume and vital capacity had been measured, the subject was given 10 per cent oxygen. The arterial saturation gradually fell during the period of exposure to the reduced oxygen concentration. After breathing the mixture for 4 minutes, 50 seconds, the saturation had fallen to approximately 85 per cent. Thereupon 100 per cent oxygen was given, the change being made abruptly. There followed a rapid rise in the saturation toward

100 per cent. The time required for this to rise from 90 per cent to 95 per cent was arbitrarily chosen as an index of the speed of the change. The lag of the galvanometer probably introduced some error in measuring the rate of increase in saturation especially when this was rapid. The galvanometer was critically damped and had a period of 4 seconds. Therefore, with a rising saturation, it would tend to record values less than the true values. However, as the saturation was rising and the galvanometer was in motion at the time a value of 90 per cent was reached, the error introduced by the inertia of the galvanometer was decreased. It was also readily demonstrated that the light spot did not swing beyond the point at which it came to rest when the selector switch was moved from one position to the other and, therefore, at times when the galvanometer was declerating, inertia would not cause it to record a more rapid rise in saturation than that which was taking place.

In the instance under consideration, the time required for the saturation to rise from 90 per cent to 95 per cent was 8.6 seconds. The average minute volume from the moment the valves were turned to admit 100 per cent oxygen, to the time when the saturation reached 95 per cent, was 12,900 c.c. The change in the base line of the respiratory complexes during administration of 100 per cent oxygen can probably be explained by the rising water vapor content of the dry oxygen which had been placed in one of the barrels only a few minutes before. The change in midcapacity due to this factor is markedly diminished when the barrels are filled 15 to 20 minutes before the test is done, and may be completely eliminated by increasing this interval to several hours.

The experiment shown in Fig. 1, *B*, which followed the first after the elapse of 45 minutes, illustrates the effect of 0.5 c.c. epinephrine 1:1000 given subcutaneously. Ten minutes after receiving the epinephrine, the expiratory reserve volume had increased by 190 c.c. and the vital capacity by over 700 c.c. Administration of 10 per cent oxygen was followed by a gradual fall in the oxygen saturation as in the previous instance, although the time required was somewhat longer (6 minutes, 50 seconds) and a saturation of 85 per cent was not quite attained. As the minute volume during this period was approximately the same as in the corresponding period in the previous experiment, the greater time suggests that epinephrine had favorably influenced pulmonary efficiency. Upon the administration of 100 per cent oxygen, 4.6 seconds were required for the saturation to rise from 90 per cent to 95 per cent even though the minute volume immediately following the change to 100 per cent oxygen was slightly less than in the corresponding period in the earlier test.

A second pair of experiments in the same patient is shown in Fig. 2. On this occasion the initial expiratory reserve volume was 310 c.c. and the vital capacity was 2,910 c.c. without medication. Ten per cent and then 100 per cent oxygen was given as in the previous experiment and the time required for the saturation to rise from 90 per cent to 95 per cent was 4.9 seconds. The increased speed in saturation compared with that observed in Test A, Fig. 1, correlates well with the larger expiratory reserve volume and vital capacity at the time of the second test (Fig. 2, *A*) and occurred even though the minute

volume here was 8,800 c.c. as compared with 12,900 c.c. in Test A, Fig. 1 during the period immediately following the administration of 100 per cent oxygen. The relative apnea that followed the administration of 100 per cent oxygen also suggests that during the hypoxic stimulus to respiration while breathing 10 per cent oxygen, excessive excretion of carbon dioxide had occurred.

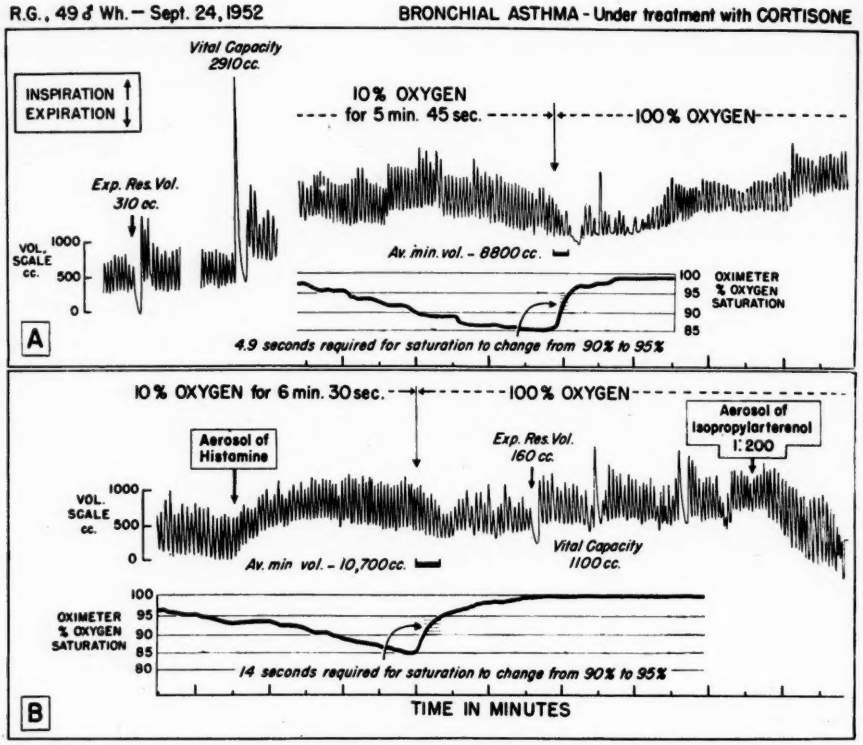

Fig. 2.—The effect of an induced asthmatic attack on the rate of rise in oxygen saturation in R. G.

Fig. 2, *B,* shows the change which was induced by the administration of an aerosol of histamine.* This was given during the period when the patient was breathing 10 per cent oxygen and the rise in the midcapacity and the temporary decrease in the tidal volume are clearly shown. Shortly after this change had taken place, the saturation reached 85 per cent. Upon the administration of 100 per cent oxygen, 14 seconds were required for the saturation to rise from 90 per cent to 95 per cent. Measurement of the expiratory reserve volume and the vital capacity immediately after this showed that these were markedly reduced, and a few minutes later the administration of an aerosol of isopropylarterenol resulted in a lowering of the midcapacity. The patient stated that he experienced moderate respiratory difficulty during this test. As in the tests shown in Fig. 1, the change in the rate of saturation varied in a manner consistent with the observed measurements of expiratory reserve volume and vital capacity.

*Made with a solution containing 20 mg. of histamine acid phosphate per cubic centimeter.

Fig. 3 shows the results of three tests done in another subject, R. D., likewise an asthmatic receiving cortisone.

In the first test (Fig. 3, *A*), the time required for the saturation to rise from 90 per cent to 95 per cent was 7.1 seconds. Immediately following this the expiratory reserve volume was observed to be 950 c.c. and the vital capacity 2,180 c.c. The patient was then given an aerosol of oak pollen extract in an attempt to produce an asthmatic attack. Perhaps because the patient, who was believed to be clinically sensitive to oak pollen on the basis of history and skin tests, had received a prolonged course of injections of

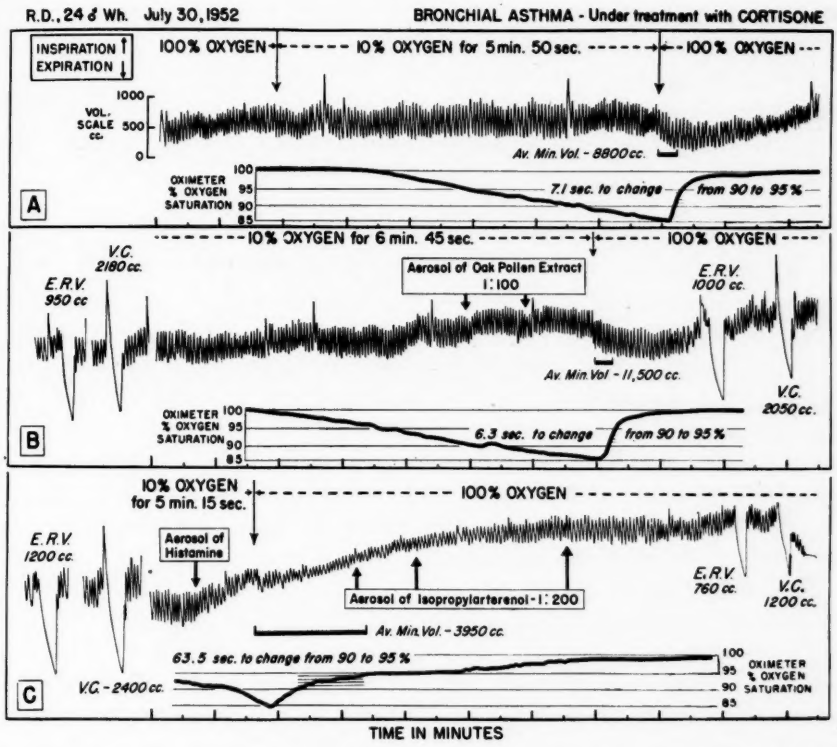

Fig. 3.—The effect of an induced asthmatic attack on tahe rate of rise in oxygen saturation in R. D.

allergenic extracts including oak pollen, no significant change occurred when the aerosol was given and, upon receiving 100 per cent oxygen, 6.3 seconds were required for the saturation to rise from 90 per cent to 95 per cent, a more rapid rise than on the first occasion. The expiratory reserve volume and the vital capacity measured immediately afterward were 1,000 c.c. and 2,050 c.c., respectively, and approximately the same figures were obtained about a half-hour later before the third test. On this occasion (Fig. 3, *C*), an aerosol of histamine was administered during inhalation of 10 per cent oxygen and a very severe attack of asthma was induced, an attack which the patient barely tolerated without interrupting the experiment. Upon receiv-

ing 100 per cent oxygen the saturation rose very slowly, requiring 63.5 seconds to rise from 90 per cent to 95 per cent. The administration of an aerosol of isopropylarterenol on three occasions in a brief space of time gave relatively little relief. In view of the rising oxygen saturation it is clear that hypoxia was not a factor in the respiratory distress which was so prominent during this attack. At the end of this test the expiratory reserve volume was 760 c.c. and the vital capacity was measured as 1,200 c.c. However, this last figure is in doubt because the supply of oxygen was exhausted immediately following this measurement. The patient stated afterward that he experienced no difficulty in obtaining sufficient air for measurement of the vital capacity and, as he was familiar with this type of test, we are inclined to assume that the measurement was valid.

DISCUSSION

Wide experience with the vital capacity and its subdivisions in patients with bronchial asthma has shown that these are markedly influenced by the degree of asthma whether spontaneous or induced. However, such measurements do not give an indication of the manner in which asthma influences the exchange of gases within the lung. Measurement of the rate at which the arterial oxygen saturation rises upon administration of 100 per cent oxygen to subjects purposely rendered hypoxic was selected for this purpose. Among 11 individuals with supposedly normal pulmonary function, the time required for the arterial saturation, as measured by the oximeter, to rise from 90 per cent to 95 per cent was consistently less than 6 seconds. In 15 patients with asthma, emphysema, or both, the time required varied from 4 seconds to 20 seconds. Those patients with the most marked respiratory disability required the longer periods and this was especially true of those with emphysema.

The results of the present study show that in the two subjects studied, changes in the rate at which induced hypoxia was relieved with 100 per cent oxygen could be readily influenced by measures designed to alter the amount of asthma present. A reduction in minute volume which may be transient commonly occurs during the induced asthmatic attack and in the second subject this may have been an important factor contributing to the marked prolongation of the time required for the saturation to rise (Fig. 3, *C*). However, as shown in Fig. 2, *B*, the reduction in minute volume was transient and, at the time the saturation was rising from 90 per cent to 95 per cent, the minute volume was greater than that recorded in the same interval in the test done before histamine was given and when the time required for the saturation to rise was less (Fig. 1, *A*). A similar lack of correlation between the minute volume and the time required for the saturation to rise is seen in the test done with epinephrine (Fig. 1). Other factors which may influence the rate of saturation are: (1) a change in the functional residual capacity; (2) a change in the manner in which the inspired gas is distributed within the lung; (3) a change in the blood-gas barrier. An increase in the functional residual capacity as shown in Figs. 2, *B* and 3, *C* is well known to occur in asthma and

might cause some delay in saturation. Uneven distribution of the inspired gas within the lung is known to be present in asthma complicated by varying degrees of emphysema,[7] but the contribution made by asthma alone to this abnormality remains to be determined. It would appear that, in the present study, such changes in distribution would satisfactorily account for alterations in the rate of saturation induced by varying the degree of asthma. There is no evidence to indicate that changes in the blood-gas barrier are associated with various degrees of asthma.

The results indicate that spontaneous asthma of minimal degree or induced asthmatic attacks, even when unassociated with more than moderate respiratory discomfort (Fig. 2, *B*), entail a measurable decrease in pulmonary efficiency as determined by the procedure described. Furthermore, these results, as well as earlier observations,[4] indicate that although the increased respiratory effort during asthma may bring about what would appear to be an adequate minute volume, this may not be sufficient to compensate for changes occurring in the lung which interfere with the exchange of gas. This may explain the common discrepancy between the degree of the patient's discomfort and the apparent adequacy of ventilation as judged by bedside observation.

SUMMARY

The rate at which the blood of asthmatic subjects, purposely rendered hypoxic, became saturated upon breathing 100 per cent oxygen was determined using the Millikan oximeter. A continuous record of respiration was obtained by having the subjects breathe in a closed system with spirometer and kymograph. The findings indicate that information concerning the functional state of the lungs may be obtained by this means. The rate of saturation was readily modified by varying the degree of asthma with epinephrine injected subcutaneously or with aerosolized histamine.

REFERENCES

1. Fowler, W. S., and Comroe, J. H., Jr.: Lung Function Studies. I. The Rate of Increase of Arterial Oxygen Saturation During the Inhalation of 100 Per Cent O_2, J. Clin. Investigation **27**: 327-334, 1948.
2. Douglas, J. C., and Edholm, O. G.: Measurement of Saturation Time and Saturation Tension With Millikan Oximeter, in Subjects With Normal Pulmonary Function, J. Applied Physiol. **2**: 307-316, 1949.
3. Alexander, R. S., and Reydman, M. M.: A Simple Test of Pulmonary Function Employing the Oximeter, J. Thoracic Surg. **25**: 95-106, 1953.
4. Lowell, F. C., Schiller, I. W., and Lowell, A.: The Use of a Closed System in the Study of Asthma and Emphysema, J. ALLERGY **23**: 335-342, 1952.
5. Lowell, F. C., Schiller, I. W., Leard, S. E., and Franklin, W.: Prolonged Treatment of Bronchial Asthma With Cortisone, J. ALLERGY **24**: 112-119, 1953.
6. Lowell, F. C., Franklin, W., Beale, H. D., and Schiller, I. W.: Occurrence of Convulsive Seizures During Treatment of Asthma With Cortisone Acetate, New England J. Med. **244**: 49-52, 1951.
7. Fowler, W. S.: Lung Function Studies. III. Uneven Pulmonary Ventilation in Normal Subjects and in Patients With Pulmonary Disease, J. Applied Physiol. **2**: 283-299, 1949.

AN EVALUATION OF TREATMENT OF RAGWEED-SENSITIVE PATIENTS WITH ADRENOCORTICOTROPIC HORMONE IN GELATIN*

JEAN ROY, M.D., ROBERT A. COOKE, M.D., AND WILLIAM B. SHERMAN, M.D.
NEW YORK, N. Y.

PREVIOUS studies have shown the value of adrenocorticotropic hormone and cortisone in the treatment of ragweed-sensitive patients.[1, 2] The purpose of this article was to study the effects of a single dose of a slowly adsorbed preparation of adrenocorticotropic hormone in fluid gelatin.

The effect of this hormone agent in the treatment of 20 ambulatory patients with ragweed hay fever and pollen asthma living in New York City or environs forms the basis of this report. The group comprised 9 male and 11 female patients; age at time of treatment varied from 12 to 55 years, with 13 of this group less than 40 years of age. The majority of the patients gave a positive family history of allergic manifestations. Members of the group gave histories of hay fever during the ragweed season for periods of from 1 to 47 years, and the diagnosis was confirmed by positive intradermal tests with ragweed extracts. Eight patients of the group also gave a history of seasonal (ragweed pollen) asthma. With respect to previous treatment, 4 patients had never received any pollen extract therapy, and 4 others had not received any injections for at least two years. The 12 remaining patients had received preseasonal or perennial therapy.

Indications for the use of corticotropin in gelatin in pollen-sensitive patients may be listed as follows: (1) those who present themselves too late for adequate preseasonal therapy, (2) those who are exquisitely sensitive to and do not tolerate adequate doses of ragweed extract, and (3) those who receive the usual injection treatment in adequate dosage but do not show satisfactory clinical improvement.

Plan of Therapy.—It was arbitrarily decided to give a single intramuscular injection of 40 mg. (or 40 Armour units) of H.P. Acthar Gel daily to each patient. The number of injections given to each patient varied from two to nineteen. It depended upon their degree of promptness of clinical improvement, the lack of cooperation of the patient, and undesirable severe side effects which occurred in 3 patients. As a control, injections of buffered saline solution were substituted for corticotropin gel for varying periods of time in 4 patients (Figs. 1 and 2).

Evaluation of Therapy.—The patients were divided into two groups. Group A comprised 12 patients with coryzal symptoms only; Group B, 8 patients with both coryza and asthma. A careful record of signs and symp-

From The Institute of Allergy, The Roosevelt Hospital.
Received for publication Aug. 1, 1953.
*Highly purified adrenocorticotropic hormone in fluid gelatin (H. P. Acthar Gel) was supplied by The Armour Laboratories, Chicago, Ill.

toms was kept for each patient during the period of observation. With two exceptions, this extended from the beginning of corticotropin injections until the end of the pollen season. The course of symptoms and clinical signs presented by each patient was arbitrarily graded from zero to 4 plus, as plotted on the accompanying Figs. 1 and 2.

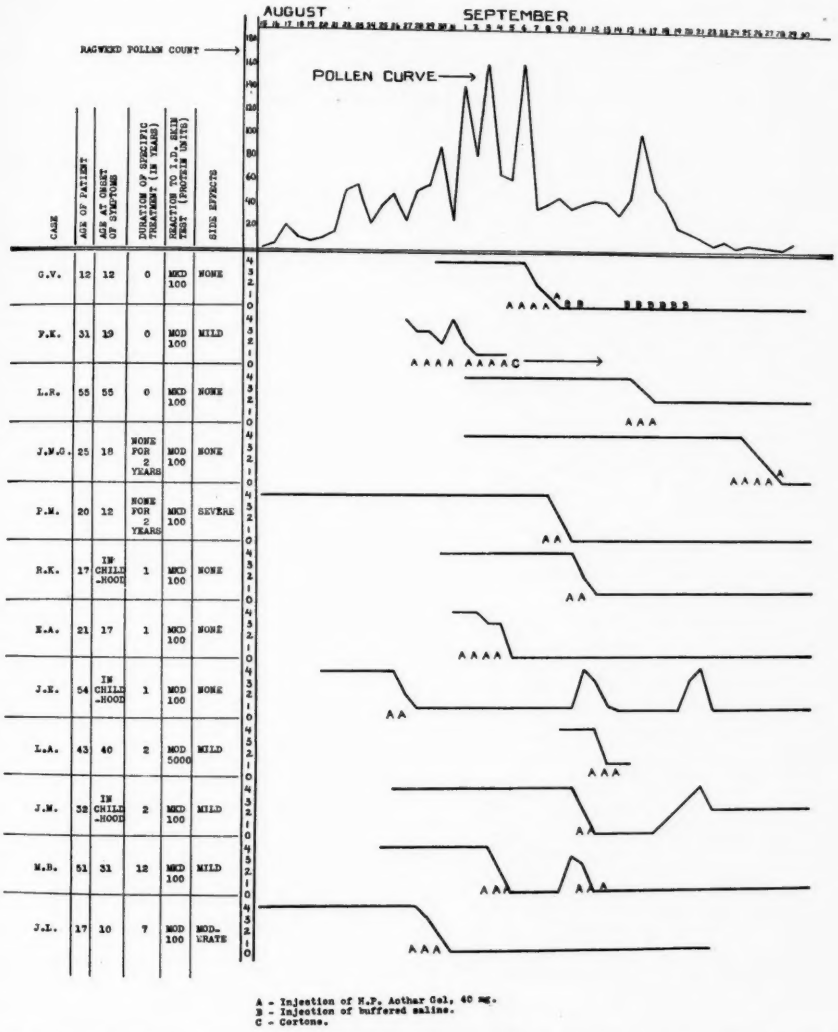
AUGUST
SEPTEMBER
RAGWEED POLLEN COUNT
POLLEN CURVE
CASE
AGE OF PATIENT
AGE AT ONSET OF SYMPTOMS
DURATION OF SPECIFIC TREATMENT (IN YEARS)
REACTION TO I.D. SKIN TEST (PROTEIN UNITS)
SIDE EFFECTS
G.V. 12 12 0 MED 100 NONE
F.K. 31 19 0 MOD 100 MILD
L.R. 55 55 0 MED 100 NONE
J.W.G. 25 18 NONE FOR 2 YEARS MOD 100 NONE
P.M. 20 12 NONE FOR 2 YEARS MED 100 SEVERE
R.K. 17 IN CHILD-HOOD 1 MED 100 NONE
E.A. 21 17 1 MED 100 NONE
J.E. 54 IN CHILD-HOOD 1 MOD 100 NONE
L.A. 43 40 2 MOD 5000 MILD
J.M. 32 IN CHILD-HOOD 2 MED 100 MILD
M.B. 51 31 12 MED 100 MILD
J.L. 17 10 7 MOD 100 MODERATE
A - Injection of H.P. Acthar Gel, 40 mg.
B - Injection of buffered saline.
C - Cortone.

Fig. 1.—Individual curves of symptoms and signs of hay fever cases graded from 0 to 4 plus.

Group A:

0 Complete freedom of subjective complaints.

\+ Stuffiness of nose; occasional sneezing and nasal mucoid discharge.

++ Mild itching sensation of nose, throat, and eyes; mild sneezing and nasal mucoid discharge.

+++ Same as ++ from mild to moderate degree; edema of nasal mucosa; hyperemia of throat.

++++ Same as +++ from moderate to a marked degree.

Group B: Plotted for asthma as follows:

0 Complete freedom of asthmatic symptoms.

+ Occasional mild wheezing.

++ Mild wheezing on exertion mostly; mild respiratory sibilants.

+++ Mild to moderate persistent wheezing and dyspnea; presence of asthmatic chest signs.

++++ Moderate to marked persisent wheezing and dyspnea; presence of asthmatic chest signs; physical activities limited.

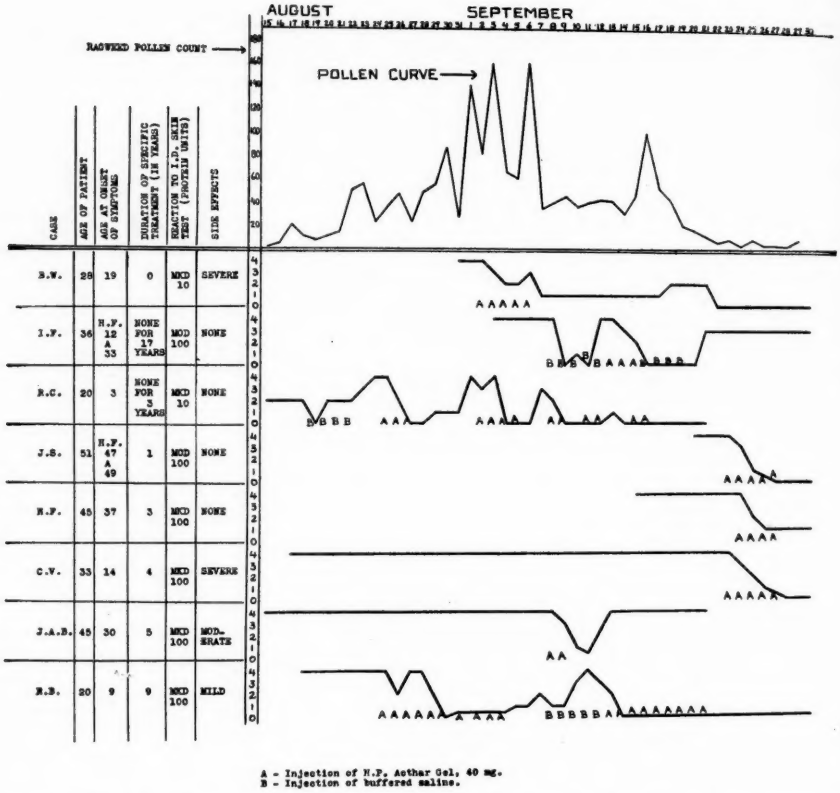
AUGUST
SEPTEMBER
RAGWEED POLLEN COUNT
POLLEN CURVE
CASE
AGE OF PATIENT
AGE AT ONSET OF SYMPTOMS
DURATION OF SPECIFIC TREATMENT (IN YEARS)
REACTION TO I.D. SKIN TEST (PROTEIN UNITS)
SIDE EFFECTS
B.W. 28 19 0 MOD 10 SEVERE
I.F. 36 H.F. 12 A 33 NONE FOR 17 YEARS MOD 100 NONE
R.C. 20 3 NONE FOR 3 YEARS MOD 10 NONE
J.S. 51 H.F. 47 A 49 1 MOD 100 NONE
H.F. 45 37 3 MOD 100 NONE
C.V. 33 14 4 MOD 100 SEVERE
J.A.B. 45 30 5 MOD 100 MOD-ERATE
R.B. 20 9 9 MOD 100 MILD
A - Injection of N.F. Acthar Gel, 40 mg.
B - Injection of buffered saline.

Fig. 2.—Individual curves of symptoms and signs of hay fever and pollen asthma cases graded from 0 to 4 plus.

Because of the small size of the group of patients studied no definitive conclusions can be reached though some interesting observations may be noted. The immediate response to corticotropin therapy appeared to be independent of age, sex, duration of disease, previous specific therapy, degree of hypersensitivity, or pollen count. There was a marked improvement in all patients within forty-eight hours after treatment was started. The majority of patients were asymptomatic after 4 or 5 successive daily injections. Most of the patients who had previously been treated with corticotropin were asymptomatic during the last peak (September 15 and 16) in the pollen count without any additional therapy.

Six patients of the rhinitis group (Group A) remained practically free of symptoms for the rest of the ragweed season after cessation of therapy. One had probably insufficient therapy and was never asymptomatic. Two had to be discarded because of insufficient follow-up and institution of cortisone therapy. The remaining 3 had recurrences of hay fever symptoms, but one responded very well to a second course of therapy (Fig. 1). The cases with hay fever and asthma appeared slightly more resistant to the action of hormone therapy and showed a greater incidence of recurrences (Fig. 2).

Side effects were noted in 10 patients, but in only 3 cases did therapy have to be discontinued (Case 5, Fig. 1, and Cases 1 and 6, Fig. 2). All side effects were temporary and disappeared promptly after cessation of therapy. Because of their subjective character, side effects were difficult to evaluate except in one patient who developed edema of both upper and lower extremities. They may be listed by order of frequency as shown in Table I. No patient

TABLE I

SIDE EFFECTS	NUMBER OF PATIENTS
Flushing of face	3
Slight headache	2
General weakness	2
Insomnia	2
Nausea	2
Dizziness	1
Lightheaded	1
Abdominal pain	1
Soreness in bones	1
Acne of face	1
Edema of extremities	1
Dryness of throat	1
Cardiac palpitation	1

complained of pain at the site of injection nor was any objective local reaction noted.

CONCLUSIONS

The clinical response of ambulatory patients with ragweed hay fever and asthma to corticotropin in gelatin has been studied.

In the group of 20 patients studied, it appeared to be an effective form of symptomatic therapy under the conditions designated.

In cases where side effects occurred they were temporary and disappeared promptly when therapy was discontinued.

The indications for the use of corticotropin gel are discussed and may be summarized: (1) patients who present themselves too late for specific therapy, (2) patients who do not tolerate pollen therapy, and (3) patients who do not respond satisfactorily to the usual treatment with pollen extract.

REFERENCES

1. Schiller, Irving W., and Lowell, Francis C.: Oral Cortisone in the Treatment of Hay Fever, J. ALLERGY **24**: 297, 1953. (See this article for other references.)
2. Randolph, Theron G., and Rollins, John P.: Adrenocorticotropic Hormone (ACTH). Its Effects in Bronchial Asthma and Ragweed Hay Fever, Ann. Allergy **8**: 149, 1950.

PROLONGED AMBULATORY USE OF CORTISONE AND ACTH FOR BRONCHIAL ASTHMA AND OTHER ALLERGIES

H. HAROLD GELFAND, M.D., NEW YORK, N. Y.

THE beneficial effects of cortisone and the adrenocorticotropic hormone (ACTH) in bronchial asthma, hay fever, urticaria, atopic dermatitis, and contact dermatitis in large series of cases[1, 2, 4-8, 10, 12, 13] have confirmed the findings of early investigators. The remarkable results produced by these hormones have not yet been adequately explained immunologically. It may be that they interfere with antigen-antibody union or alter the cell reaction so as to prevent the release of histamine. But whatever the mechanism, the clinical relief following their use is definite, and at times even dramatic.

The purpose of this paper is to report the results obtained from prolonged administration of cortisone and ACTH in a large group of ambulatory patients with bronchial asthma and allied allergies. The study was undertaken in order to explore the following questions: (1) whether the action of the hormones is direct and therefore specific; (2) whether prolonged treatment can be tolerated by allergic patients; (3) whether routine use in ambulatory patients is practical; and (4) whether it benefits the condition sufficiently to justify its continuation over long periods of time.

During the study we developed a therapeutic regimen in which cortisone and ACTH were given in combination in a manner to be described. This appeared to produce optimum results in a large number of ambulatory patients both in the allergy clinics and in our office practice. No attempt will be made here to record all the cases treated; the protocol and case histories which will be presented cover only a small number of typical cases, eighteen of bronchial asthma and nine of allergic dermatitis.

PLAN OF STUDY

Most of the patients selected for hormonal treatment were suffering from severe allergic diseases which had persisted over a period of years and had resisted conventional methods of therapy. Therefore we decided to employ this new clinical approach, using cortisone orally in the form of Cortone* tablets or ACTH intramuscularly. For the past eighteen months we have been giving the two hormones in combination. The patients were started on cortisone and the dosage was gradually reduced as improvement appeared. ACTH was given about twice a week, either to strengthen the beneficial effects of cortisone or during the tapering-off period when a maintenance level was being determined. Once established, the maintenance dosage was continued for long periods of time.

From the Departments of Medicine and Allergy, Gouverneur Hospital, New York, N. Y.
Read before the monthly clinical staff meeting of Gouverneur Hospital on May 20, 1952.
Received for publication April 10, 1953.

*Cortone is the trade name adopted by Merck and Company, Inc., manufacturers of cortisone.

ACTH was injected in the form of a gel, when this became available, as a means of prolonging the hormonal action. In a few of the cases to be presented, cortisone was given by intramuscular injection, and in a few others ACTH was used alone. During hormonal therapy standard measures were continued and the search for specific allergens carried on where indicated.

In order to observe any untoward effects of the hormones, we examined each patient at least three times a week for weight gain, periorbital edema, or edema of the face. The urine was tested for sugar at regular intervals. The blood pressure was checked two or three times a week. These patients were asked to follow the pattern of low sodium intake, but were not restricted to absolute figures. There was no need for the addition of potassium. There were no clinical symptoms of possible potassium deficiency. The screening procedure used in the selection of proper cases for hormonal therapy was as stated previously: patients suffering from severe allergic diseases which had persisted over a period of years and had resisted conventional methods of therapy and patients suffering from the severe intractable form of asthma or the severe acute phase of allergic dermatitis who were not financially prepared for hospitalization, or cases where a hospital bed was not available at the time. Thus, to help carry the patient over the acute phases of the bronchial asthma or the acute phase of the dermatitis we employed this new clinical approach.

DOSAGE

For severe cases of bronchial asthma or dermatitis, it was found that an initial dosage of cortisone of 200 mg. daily was required for the first few days. Upon improvement this was stepped down to 100, 75, 50, and 25 mg., with a final maintenance dosage as low as would keep the patient symptom-free, usually 12.5 mg. daily or every other day, accompanied by 10 or 20 units of ACTH gel once or twice a week. Less severe cases responded well to initial daily doses of 100 or even 75 mg. of cortisone, reduced gradually to a low maintenance dose of 12.5 every two or three days, usually with but sometimes without the addition of ACTH gel. However, we believe that optimum results are obtained by giving 10, 20, or 40 units of the gel once or twice a week during the tapering-off period.

SIDE REACTIONS

This method of using relatively low doses gradually decreased and supplemented with ACTH appears to reduce the incidence of side reactions. No single instance of Cushing's syndrome occurred in this series. Two patients gained some weight but showed no evidence of fluid retention; their general symptomatic improvement and feeling of well-being led to increased appetite and consequent weight gain. One of these (not listed here) also had a rise in blood pressure during treatment, but it never reached dangerous levels and reverted to normal when the hormones were withdrawn. In two cases treatment was discontinued because of exacerbation of pre-existing illness: one patient with cardiac disease (Case 17) developed active symptoms, and one with a dormant psychosis (Case 25) suffered a flare-up. Sugar showed in the urine of one

patient (Case 27) as a direct result of cortisone, and the hormone was withdrawn for this reason. Other reactions were mild and infrequent, consisting of sweating, slight numbness and tingling of the extremities, abdominal distention, nervous tension, palpitation, and hot flashes.

Most of the patients have now been on hormonal therapy for nearly two years and are being continued on low doses where necessary. If weakness sets in or if hypopotassemia is feared, the patients are either denied the hormones or are given potassium chloride orally. However, no instance of proved potassium depletion has thus far been observed in this series.

THERAPEUTIC RESULTS

In the larger series of patients treated, the therapeutic results of the two hormones were extremely gratifying, especially when they were used in conjunction as described. In the twenty-seven cases presented here, it will be seen that the vast majority were rapidly relieved of symptoms and that recurrences also responded well when they appeared. Since the symptomatic improvement was evident clinically, there was no need for vital capacity or other studies for corroboration.

Of the eighteen patients with bronchial asthma, only one (Case 14) failed to show any considerable improvement. In two (Cases 11 and 13), the patients were for various reasons unable to remain under continuous treatment: one of these (Case 11) had made a poor response to cortisone but improved with ACTH; the other (Case 13), who had multiple sensitivities, responded well to cortisone both in a first course and in the treatment of a recurrence, but failed thereafter to take the hormone regularly, so that final results were considered only fair.

All of the nine cases of allergic dermatitis cleared up in a highly satisfactory manner under treatment. Most of the conditions were very severe and protracted. One patient (Case 20), who was sensitive to a number of foods, had urticaria and angioedema, which responded to the first 100 mg. of oral cortisone. Another (Case 21) had widespread contact dermatitis and urticaria due to multiple contactants and ingestants, and required prolonged treatment for the original lesions and for two recurrences, but was finally relieved of symptoms, and keeps well on a low maintenance dosage. A cosmetician (Case 19), sensitive to many substances encountered in her work, responded rapidly to cortisone alone and has been able to carry on with her job. Two of the patients with allergic dermatitis also had asthma, and both conditions improved under treatment. All of the patients who were able to continue with hormonal therapy are keeping well either by means of maintenance doses or by retreatment of recurrences as they appear.

ASTHMA

The patients in this group ranged in age from 12 to 70 years and had suffered from some form of allergy for two to twenty-five years. The etiology varied as follows: (1) sensitization to inhalants, foods, drugs, or bacteria; (2)

secondary to infection in sinuses, teeth, or tonsils; (3) combined causes; and (4) unknown. Most of the patients had failed to respond satisfactorily to standard treatment before hormonal therapy was begun.

As a rule, before the hormones were started, the patients were given a thorough physical examination including x-ray examination of the chest, sinuses, and teeth and transillumination of the sinuses. Purulent material, when present, was removed from the nose, pharynx, tonsils, and sinuses and studied both microscopically and by culture. Autogenous vaccines were prepared and introduced into the therapy when indicated. Intracutaneous tests for sensitivity were completed. Food elimination tests by food, diary, and other methods were given in cases of food allergy. On the basis of the findings, patients were asked to change their environment or diet, and immunization procedures were started. If they failed to respond to these measures, hormonal therapy was instituted.

CASE REPORTS

The results of treatment in the eighteen cases are shown in Table I, but certain representative histories will be given in greater detail.

CASE 3.—S. B., a 40-year-old woman, had had severe asthma for two years. Etiology included various foods and inhalants. Cortisone (Cortone Inpectable) was given intramuscularly, beginning in January, 1951, in a daily dosage of 100 mg. for four days, 75 mg. for three days, and 50 mg. for two days. After nine days of treatment the patient was sufficiently improved to be put on a maintenance regime of 25 mg. daily for seventeen days, then three times a week, then twice a week. After two and one-half weeks of treatment she began to feel definite relief of symptoms. The course covered nearly four months, and was then ended.

Symptoms recurred after a lapse of five and one-half months and treatment was reinstituted in October, 1951, with oral cortisone in a daily dosage of 100 mg. for three days, 75 mg. for two days, 50 mg. for two days, and 25 mg. for fourteen days. The tapering-off dosage was supplemented toward the end by 10 units of ACTH gel injected twice a week. Immunization therapy against dust, feathers, and several pollens was given concomitantly. No side reactions occurred and there was complete relief of symptoms. When last seen in December, 1952, the patient was doing well.

CASE 4.—M. H. was a woman 44 years old. The duration of asthma was thirteen years. Etiology included various pollens, dusts, and foods. Cortone Injectable was begun in January, 1951, on the following schedule: first week, a total of 500 mg. in divided doses; second week, 200 mg.; third week, 200 mg.; fourth and fifth weeks, 100 mg. weekly. After receiving a grand total of 1,025 mg., the patient was sufficiently improved to be put on a maintenance dosage of 25 mg. three times a week.

She did well until January, 1952, when the asthma returned. Oral cortisone was then begun in a daily dosage of 100 mg. for four days, 75 mg. for three days, 50 mg. for two days, and 25 mg. for fifteen days, reaching a total of 1,100 mg. At this time the patient felt completely relieved. She was placed on a decreasing maintenance dosage of 75 mg. per week for two weeks, then 50 mg. per week. Immunization therapy also was given. The results were good. It was gratifying to note that this prolonged administration of hormones produced no untoward reactions.

CASE 5.*—N. N., a man of 33, had intractable pollen asthma of nineteen years' duration, due to grass and ragweed pollens. Oral cortisone was begun in May, 1952, in a

*It should be stated that the patients in Cases 5, 11, and 14 referred to in this article, who were treated with the corticosteroids, also received the usual standard measure of hyposensitization therapy with the allergens to which they were found sensitive. These patients were also regularly instructed to avoid contact with, or the ingestion of, known allergens

TABLE I. ASTHMA

18 CASES OF BRONCHIAL OR POLLEN ASTHMA TREATED WITH CORTISONE AND/OR ACTH

CASE NO. AND INITIALS	AGE AND SEX	ETIOLOGY AND DURATION OF ASTHMA	TREATMENT†	THERAPEUTIC RESULTS	UNTOWARD REACTIONS
1, R. T.	60 F.	Infected antrum; foods, inhalants, 15 yr.	Oral Cortone mg./day: 150-75. Maintenance, 25 mg./day for 5 mo., then discontinued. Occasional attacks controlled with 50 mg.	Excellent	Moderate weight gain, slight numbness of arms
2, H. L.	34 F.	Several inhalants and ingestants, 2 yr.	Oral Cortone mg./day: 75-50-25. Maintenance 10 mg./day plus ACTH gel 20 u./wk. Immunization	Excellent	None
*3, S. B.	40 F.	Many ingestants and inhalants, 2 yr.	Cortone Injectable I. M. mg./day: 100-75-50. Maintenance, 25 mg./day, then 3 times/wk., then 2 times/wk. Recurrence treated with oral Cortone in similar dosage. Maintenance dose supplemented with ACTH gel 20 u./wk. Immunization	Excellent	None
*4, M. H.	44 F.	Variors pollens, dusts, foods, 13 yr.	Cortone Injectable mg./wk.: 500-200-100. Maintenance, 25 mg. 3 times/wk. Recurrence treated with oral Cortone mg./day: 100-75-50-25. Maintenance, 75-50 mg./wk. Immunization	Good	None
*5, N. N.	33 M.	Grass and ragweed pollens, 19 yr.	Oral Cortone mg./day: 100-75-50. Maintenance, 50 mg., later 75 mg./day plus ACTH gel 40 u./wk.	Good	Slight tingling numbness of mouth and fingers; slight palpitation; hot flashes with large doses
6, E. K.	46 F.	Infected antrum; inhalants, ingestants, 2 yr.	Oral Cortone mg./day: 200-150-75-50-25. Maintenance, 12.5 mg./day plus ACTH gel 10 u. 2 times/wk. Recurrence controlled by doubling maintenance doses	Excellent	None
*7, C. C.	12 F.	Numerous inhalants and ingestants, 11 yr. (Also recurrent eczema, *see* Table II, Case 22)	Oral Cortone mg./day: 50-25-12.5. Maintenance, 12.5 mg. every 2 days. Immunization	Excellent (both conditions relieved)	None

8, S. T.	19	F.	Numerous inhalants, 4 yr.	ACTH gel 120 u. for 1 wk., then 70 u. for 1 wk. Maintenance, oral Cortone 75 mg./day	Excellent	None
9, H. L.	38	F.	Infected antra and ethmoids; numerous inhalants, 7 yr.	ACTH alone, 40 u./day for 2 days	Excellent	None
10, J. S.	67	M.	Various inhalants and ingestants, 2 yr.	Oral Cortone 75 mg./day plus ACTH 160 u., then 80 u./wk. Maintenance, oral Cortone 75 mg./day	Excellent	None
*11, M. N.	16	F.	Various inhalants and ingestants, 7 yr.	Cortisone for 3 wk., in hospital; then ACTH 4 times daily for 10 days. At office, a total of 425 mg. of oral Cortone in 13 days. Treatment discontinued	Poor with Cortone, good with ACTH	Sweating after cortisone
12, M. B.	64	F.	Many inhalants and ingestants, 2 yr.	Oral Cortone mg./day: 100-75-50. Recurrence treated with 75 mg./day. Maintenance, 10 mg./day plus ACTH gel 20 u. 4 times/wk.	Excellent	None
13, B. P.	47	F.	Many inhalants and ingestants, 21 yr.	Cortone Injectable mg./day: 200-100-75-50. Maintenance, 200 mg. wk. Recurrence treated with oral Cortone mg./day: 100-75-50. Maintenance, 25 mg./day. Immunization. (Patient did not take treatment regularly)	Fair	None
*14, M. G.	49	M.	Pollens, 25 yr.	Oral Cortone mg./day: 200-100-75. Treatment stopped after 4 wk.	Poor	Abdominal distention
15, B. S.	53	F.	Numerous inhalants, 15 yr.	Oral Cortone mg./day: 100-75-50. Maintenance, 25 mg./day plus ACTH gel 20 u./wk.	Excellent	None
16, P. H.	55	M.	Numerous inhalants and ingestants, 6 yr.	Oral Cortone mg./day: 100-75-50-25. Maintenance, 25 mg. every 2 days plus ACTH gel 20 u./wk.	Excellent	None
17, J. W.	70	M.	Various inhalants, 20 yr.	Oral Cortone mg./day: 100-50-25. Hormone discontinued after 2 wk.	Excellent	Exacerbation of existing cardiac disease: arythmia, cyanosis, etc.
18, N. B.	48	M.	Infection, 40 yr. (Also allergic dermatitis due to inhalants for 2 mo., *see* Table II, Case 26)	ACTH gel 40 u. 3 times/wk.	Excellent, both conditions relieved	None

*Described in text.

†A step-down dosage was given. When improvement appeared, which was usually after a few doses of hormone, the dosage was gradually reduced until a low maintenance level was established. This was often continued for several months, but some patients did well without further hormones after initial recovery. Recurrences usually responded to a new course of hormones or to one or two single doses.

daily dosage of 100 mg. for one week, 75 mg. the next week, then 50 mg. for two weeks supplemented by ACTH gel, 20 units twice a week. Since the maintenance dose of cortisone proved inadequate, it was raised to 75 mg. daily. The patient began to improve after he had received the first 200 mg. of Cortone, and he finally became symptom-free. Side reactions noted were tingling of the tongue, palate, and fingers, with slight numbness, slight palpitation of the heart, and hot flushes caused by large doses of cortisone. At present while in the city the patient feels comfortable; when planning a trip to the country in the height of the pollen season, he asks for a supplementary injection of ACTH gel. Twenty units affords protection under exposure for twenty-four to thirty-six hours, and 40 units for forty-eight hours.

CASE 7.—C. C., a girl of 12, had suffered with asthma from infancy which was accompanied by recurrent attacks of eczema, due to inhalants (dust, pollens, feathers, wool, tobacco) and ingestants (eggs, liver, fish). Oral cortisone was begun in April, 1952, with 50 mg. daily for two days, and 12.5 mg. for three days, then 12.5 mg. every other day as a maintenance dose; desensitization was given concurrently with complete relief of the asthma. (The eczema responded later, as recorded in Case 22.) There were no side reactions.

CASE 11.—M. N., a 16-year-old girl, had had intractable bronchial asthma for seven years due to inhalants (kapok, dust) and ingestants (spices, fried foods). This patient was at first hospitalized and given cortisone for three weeks with only slight benefit, but she responded well to daily injections of ACTH for ten days. Symptoms returned after ACTH was discontinued. Office treatment was begun in January, 1951, with oral cortisone. A total of 425 mg. given over a period of thirteen days produced no satisfactory improvement. The patient was unable to afford ACTH, and treatment was discontinued. She later moved to Arizona, where she did well. The results of therapy were excellent with ACTH, poor with cortisone. A side reaction was sweating after cortisone.

CASE 14.—M. G., a man 49 years old, had had pollen asthma persisting for twenty-five years. Cortone tablets were administered in a dosage of 200 mg. daily for two weeks. After he had received 800 mg., the patient seemed to feel some improvement. For the next two weeks the daily doses were 100 mg. and 75 mg., respectively. The results in this case were poor, and the complication of abdominal distention was encountered.

ALLERGIC DERMATITIS

Except for one girl 12 years old, all of these patients were adults in early or middle life, the oldest being 59 years. Their lesions usually were due to multiple sensitivities and had persisted, often with remissions, for periods of two months to fifteen years. The etiology included inhalants, ingestants, and contactants. Two of the patients (Cases 22 and 26) were also suffering from asthma. Previous treatment had failed to control the symptoms to any satisfactory degree. As noted before, hormonal therapy gave good to excellent results in all of the cases, although it had to be discontinued, after notable relief had been obtained, in two patients because of untoward reactions.

CASE REPORTS

The nine cases are summarized in Table II, and some of them are described in detail because of special interest.

CASE 19.—S. P. was a woman 46 years old, with contact dermatitis of eight years' duration due to tragacanth, gum arabic, and Roux hair dye, which she used in her work as

TABLE II. ALLERGIC DERMATITIS. 9 CASES TREATED WITH CORTISONE AND/OR ACTH

TABLE II. ALLERGIC DERMATITIS. 9 CASES TREATED WITH CORTISONE AND/OR ACTH

CASE NO. AND INITIALS	AGE AND SEX	TYPE, ETIOLOGY, AND DURATION	TREATMENT	THERAPEUTIC RESULTS	UNTOWARD REACTIONS
*19, S. P.	46 F.	Contact dermatitis due to vegetable gums, hair dye, 8 yr.	Cortone Injectable 50 mg. a day, then oral Cortone mg./day: 100-75-50. Maintenance, 12.5 mg./day	Excellent	None
20, T. T.	50 F.	Urticaria, angioedema, due to numerous foods, 1 yr.	Oral Cortone mg./day: 100-75-50-25. No maintenance dose. Recurrences controlled by 25 or 50 mg.	Excellent	None
*21, F. W.	60 F.	Contact dermatitis, urticaria, pruritus, due to several contactants and ingestants, 6 mo.	Cortone Injectable mg./day: 200-150-100-80. No maintenance. Recurrence after 1 yr. treated with oral Cortone mg./day: 50-25-12.5. Second recurrence treated with ACTH gel 40 u./wk. plus Cortone 100 mg./wk., then Cortone alone 75 mg./day. Maintenance, 25 mg./day.	Excellent, patient remains well without hormones	None
22, C. C.	12 F.	Recurrent eczema due to many inhalants and ingestants, 11 yr. (also asthma, *see* Table I, Case 7)	Oral Cortone mg./day: 50-25-12.5. Maintenance, 12.5 mg. every 2 days. Immunization	Excellent (both conditions relieved)	None
23, M. C.	42 F.	Recurrent urticaria due to ingestants (7 common foods), 2 yr.	Oral Cortone mg./day: 75-50-25. Maintenance, 25 mg. every 2 days plus ACTH gel 20 u. 4 times/wk., then 10 u. 4 times/wk.	Excellent, patient remains well without hormones	None
24, B. S.	57 F.	Recurrent urticaria and angioedema due to numerous inhalants and ingestants, 13 yr.	Oral Cortone mg./day: 100-75-50-25. Maintenance, 5 mg./day plus ACTH gel 20 u., then 10 u./wk.	Excellent	None
25, M. B.	17 M.	Weeping eczema due to various inhalants and foods, 15 yr.	Cortone Injectable mg./wk.: 350-200-100. Treatment stopped after 4 wk.	Excellent	Flare-up of dormant psychosis
26, N.B.	48 M.	Dermatitis due to numerous inhalants, 2 mo. (also bronchial asthma of infectious origin, *see* Table I, Case 18)	ACTH gel alone, 40 u. 3 times/wk.	Excellent, both conditions relieved	None
27, H. B.	59 M.	Dermatitis due to numerous inhalants, 4 yr.	Oral Cortone mg./day: 75-50, the latter dosage supplemented by ACTH gel 40 u. in 1 wk. Hormones discontinued after 10 days	Good	Sugar in urine

*Described in text.

cosmetician. Cortone Injectable was given in a dosage of 25 mg. daily for one week (total 350 mg.); oral cortisone was given at the rate of 25 mg. four times a day for four days, then three times a day for three days, then twice a day for two days. On a final maintenance dose of 12.5 mg. per day, the symptoms have been completely controlled. The patient has continued at her job, advoiding as much as possible direct contact with the specific irritants. The results were excellent and there were no side reactions.

CASE 21.*—F. W., a 60-year-old woman, suffered from contact dermatitis and urticaria involving elbows, thighs, hips, and vagina, accompanied by rectal and vaginal pruritus. Etiology included contactants (perfume, wool, nylon) and ingestants (barbiturates, chocolate). The condition had persisted for six months and was intractable to standard treatment. In January, 1951, cortisone was given by injection in daily doses of 200 mg. for three days, 150 mg. for three days, 100 mg. for seven days, and 80 mg. for seven days. By the twelfth day of treatment the symptoms had disappeared. There was a recurrence about one year later (February, 1952), and 25 mg. of oral cortisone was administered twice daily for two weeks, then once a day for two weeks, followed by 12.5 mg. daily for three months. After a total of 1,612 mg. (1.6 Gm.) had been given, there was a complete resolution of all the lesions. On a second recurrence, ACTH gel, 40 units per week, was given in conjunction with 100 mg. of cortisone daily for three weeks. ACTH was then stopped and cortisone continued at the rate of 75 mg. daily for seven days. Following this, the patient was put on a maintenance dosage of 25 mg. per day and remained symptom-free. When last examined in January, 1953, she was keeping well without the hormones. There were no side reactions, despite prolonged treatment.

DISCUSSION

In view of the favorable results from hormonal therapy reported by many investigators, the question arises—how are these results accomplished? What is the mechanism of action of cortisone and ACTH in allergic disease? Is the immunologic mechanism altered? Are the antibodies changed? Is the positive skin reaction abolished, or the histamine reaction? These matters have been explored with the following results:

1. The direct skin reactions to inhalants remain the same after hormonal therapy. Some observers have reported a slight reduction of the wheal, but one so slight as to be almost imperceptible, and no change in the skin response to histamine.[2, 3, 5, 14, 15]

2. The passive transfer findings remain the same.[5, 15]

3. The greatest change is in the tissue that shows the greatest malfunction.

Cooke and his associates observed one definitive change in cases of bronchial asthma by electrophoretic studies, namely, an alteration in the albumin and globulin serum fractions.[4] In intractable asthma their studies indicated a definite deviation from the normal pattern: serum albumin becomes low; alpha 1 and alpha 2 globulin rise and later return to normal; the beta globulin fraction remains around normal; and gamma globulin first rises and then returns to normal. The total protein does not change. There is no change in cell volume. When hormonal therapy is given and the patient improves clinically, a return to the normal pattern is evidenced by this method.

*It should also be stated here that Case 21 while being treated with Cortisone and ACTH as described in the text was also followed and treated carefully with regard to the allergens to which this patient was found sensitive. Thus avoidance measures and actual hyposensitization therapy were strictly adhered to.

Further serologic studies by this group[9] have been made on patients with chronic infectious asthma and intrinsic dermatitis, using chemical and electrophoretic techniques. The patterns in many sera have shown a distinctly abnormal distribution of the various protein fractions, albumin, alpha 1, alpha 2, and beta and gamma globulins. This group further suggests that "these changes are not the result of the allergic state per se, but apparently are related directly or indirectly to the chronic underlying infection, since similar alterations of protein distribution are found in such chronic nonallergic infections as osteomyelitis and bronchiectasis. The changes are comparable to the profound changes reported by Reiner[11] in lupus erythematosus, where there is a lowering of the albumin and a rise in the alpha globulin fraction."

PRACTICAL CONSIDERATIONS

We are now able to state definitely that the use of the steroid hormones, cortisone, and ACTH produces spectacular clinical results in bronchial asthma, pollen asthma, and allergic dermatitis. The control of symptoms is of distinct value to the patient as well as to the physician in the following ways:

1. Hormonal therapy produces rapid remission in subjects suffering from prolonged and intractable symptoms. In severe bronchial asthma of the status type it removes at once the unpredictability and acute anxiety characteristic of this condition. Thus it opens up an avenue for the application of additional forms of treatment which serve to maintain the improvement and permit the natural resistance of the patient to come to the fore. In utilizing hormonal therapy we do not assume a dogmatic attitude, discarding time-honored forms of treatment in favor of the new. On the contrary, we use all the means at our command to supplement one another, with the hope of producing lasting relief.

2. Hormonal therapy permits reorganization and rehabilitation of the patient and the search by skin nad other tests for the etiological agent. It also permits time for the removal of irritants from the patient's environment, the elimination of foci of infection, and the institution of immunization procedures to sustain the therapeutic effects. By these means we can overcome or forestall dehydration and improve the patient's nutrition.

3. By the continued use of hormones at whatever the maintenance level may be in the particular case, plus the standard therapeutic regimes, we believe that these patients may thus be greatly benefited, and return to normal life at the earliest possible time.

SUMMARY AND CONCLUSIONS

Eighteen cases of bronchial asthma and nine cases of allergic dermatitis treated with cortisone or ACTH or both have been described. These cases were selected from a much larger series, of which they were considered representative. Most of them had proved intractable to other modes of therapy. The etiological factors included inhalants, contactants, ingestants, and infections. Excellent results were obtained in all but three of the eighteen cases of asthma and in all of the nine cases of allergic dermatitis. In fact, there was only one true failure; in the other two cases good or fair results were achieved initially but the patients

did not continue with the treatment. Remission of symptoms usually was maintained by the application of standard therapy, such as removal of the patient from specific irritants, change of diet, elimination of infectious foci, and immunization, plus small maintenance doses of the hormones, usually of oral cortisone supplemented by ACTH gel. Side reactions were infrequent, and in only three cases were they serious enough to call for withdrawal of the hormones.

The dosage of steroid hormones should be the lowest that will bring about a rapid relief of symptoms, after which gradually decreasing doses can be given. Some patients do well after a few weeks' hormonal therapy supplemented by standard measures. Others require a maintenance dose of cortisone at a very low level for long periods of time, often combined with weekly or semiweekly injections of ACTH. Complete and sudden discontinuance should be avoided to guard against the exhaustion state. Tapering off can best be accomplished first by a gradual reduction in the daily dose, then by an increased interval between doses. The relatively low dosages required minimize the untoward reactions often produced by the steroid hormones.

While the mode of action of these hormones in allergy is not known, their clinical usefulness in bronchial asthma, pollen asthma, and allergic dermatitis is well established. For patients in status asthmaticus or with severe pollen asthma, this treatment provides physical and mental rest, thus permitting improved nutrition and hydration when these are most needed. The results in allergic dermatitis appear to be exceptionally good and can be obtained with comparatively small doses. However, there is no evidence that the hormones influence the further course of allergic diseases or that either arrest or complete cure is achieved after they have been discontinued. It is only when maintenance therapy is continued for long periods that the benefits are long lasting, covering many months to more than one year. Clinical symptoms recur sooner or later after the hormones have been completely withdrawn unless the irritating factor is eliminated.

Nevertheless, from all the data that have been accumulated, it may safely be concluded that the steroid hormones, properly used, constitute one of the most important new additions to the allergist's armamentarium.

REFERENCES

1. Arbesman, C. E., Schneider, M. A., Greene, D. G., and Osgood, H.: Intravenous ACTH and Oral Cortisone in the Treatment of Bronchial Asthma, J. ALLERGY **23**: 293-302, 1952.
2. Baldwin, H. S., and DeGara, P. F.: Hospital and Ambulatory Treatment of Asthma and Eczema with ACTH and Cortisone, J. ALLERGY **23**: 15-16, 1952.
3. Bowman, K. L., Seigel, B. B., and Walzer, M.: The Influence of a Single Dose of ACTH on the Atopic and Histamine Skin Reactions, J. ALLERGY **23**: 130-139, 1952.
4. Cooke, R. A., Sherman, W. B., Menzel, A. E. O., Chapin, H. B., Howell, C. M., Scott, R. B., Myers, P. A., and Downing, L. M.: ACTH and Cortisone in Allergic Diseases: Clinical, Serologic (Electrophoretic), and Immunologic Studies, J. ALLERGY **22**: 211-236, 1951.
5. Feinberg, S. M., Dannenberg, T. B., and Malkiel, S.: ACTH and Cortisone in Allergic Manifestations: Therapeutic Results and Studies on Immunological Tissue Reactivity, J. ALLERGY **22**: 195-209, 1951.
6. Fontana, V. J.: Asthma in Children: A Review of the Recent Literature, J. ALLERGY **23**: 465-477, 1952.

7. Gay, L. N., and Murgatroyd, G. W., Jr.: A Clinical Report on the Treatment of Contact Dermatitis With Adrenocorticotropic Hormone in Oil, J. ALLERGY **23**: 215-221, 1952.
8. Hampton, S. F.: Intravenous ACTH in the Treatment of Allergic Diseases, J. ALLERGY **23**: 493-503, 1952.
9. Menzel, A. E. O., Kessler, W. R., Cooke, R. A., and Myers, P.: Immunoserologic Studies of the Immediate Wheal-type Allergies, J. ALLERGY **23**: 483-488, 1952.
10. Mitchell, H. S., and Cameron, G.: Cortisone in Asthma, Canad. M. A. J. **66**: 313-316, 1952.
11. Reiner, M.: Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus, Proc. Soc. Exper. Biol. & Med. **74**: 529-531, 1950. (Quoted by Cooke.[4])
12. Tillman, H. B.: The Management of Bronchial Asthma, New England J. Med. **247**: 163-166, 1952.
13. Unger, L., and Unger, A. H.: Treatment of Bronchial Asthma, J. A. M. A. **150**: 562-569, 1952.
14. Rose, B., Pare, J. A. P., Pump, K., and Stanford, R. C.: Preliminary Report on Adrenocorticotropic Hormone (ACTH) in Asthma, Canad. M. A. J. **62**: 6, 1950.
15. Zeller, M., Randolph, T. G., and Robbins, J. P.: Adrenocorticotropic Hormone (ACTH), Gross and Histologic Effects on the Skin Tests and Passive Transfer, Ann. Allergy **8**: 163, 1950.

SENSITIVITY TO CORNSTARCH

A Case Report

Aaron D. Spielman, M.D., New York, N. Y.

RANDOLPH and Yaeger[1] have stressed the importance of corn and its refined derivatives as sources of allergic symptoms, placing it near the top of the list of important food allergens along with wheat, milk, and eggs. They claim that corn sugar can also act as an excitant, stating: "In fact, the highly sensitive patient, otherwise controlled as far as his corn allergy is concerned, will usually react with more immediate symptoms following the ingestion of corn sugar than he will from eating cornstarch, corn as such, or corn oil."

Bernton[2] was unable to confirm the high incidence of corn allergy reported by the above workers, finding only one-fifth as many cases in spite of employing Randolph's diagnostic procedure accurately. Bernton could find no evidence for sensitivity toward corn syrup or sugar. Loveless,[3] in a survey of American allergists, encountered only 0.16 per cent of some 45,000 patients who gave clinical reactions to ingested corn. This figure stood in marked contrast to the figures of 16 to 30 per cent reported by Rinkel, Randolph, Rowe, and Crandall.[2] When blindfold ingestion tests were carried out in association with placebo meals for twenty-five individuals who gave histories suggestive of corn allergy, no instance of susceptibility for corn syrup, sugar, or oil could be found by Loveless and a number of cases of psychogenic response were uncovered. It was of interest that a few of these subjects reacted convincingly to one or more of the three starches employed in the masked feedings. The purpose of the present article is to report the findings on another such patient who was studied with the Loveless technique and was shown to be allergic to cornstarch but fully tolerant of corn sugar.

CASE REPORT

Miss A, aged 40, gave a history of atopic eczema during a ten-year period ending at the age of 18 years. She had also suffered migraine attacks since early childhood. At 22 she began to have symptoms suggestive of ulcer and colitis, which responded to antihistamines given when she was 36 years of age. At 40 the skin was found to respond to tests with lemon, rye, onion, and corn meal. Omission of these foods from the diet resulted in marked relief of all symptoms.

With reference to corn, she had noted that even small amounts of cornstarch provoked a tingling and burning sensation of the tongue promptly. Nausea, abdominal colic, and diarrhea soon ensued. Marked fatigue and a sense of mental dullness were accompanying complaints and were associated with difficulty in focusing the patient's vision. The patient believed that corn syrup led to mild symptoms of similar nature.

Blindfold ingestion tests with the Loveless coded puddings* were given this patient on five separate occasions; the contents of the indistinguishable meals were unknown to both

Received for publication, May 4, 1953.

*The puddings were kindly supplied by the National Starch Products through the courtesy of Mr. Vincent Marsilia.

TABLE I

DATE OF INGESTION TEST	COMPOSITION OF PUDDING		ALLERGIC SYMPTOMS	TIME OF ONSET P. C.
	STARCH	SWEETENER		
10/6/51	Tapioca	Cane sugar	None	
10/12/51	Corn	Cane sugar	(1) Tingling and burning of tongue +++	Immediate
			(2) Nausea +++	¼ hr.
			(3) Abdominal cramps ++	¼ hr.
			(4) Fatigue +++	¼ hr.
10/26/51	Arrowroot	Cane sugar	Tingling sensation of tongue +	¼ hr.
11/9/51	Corn	Corn syrup	(1) Tingling and burning of tongue +++	Immediate
			(2) Nausea +++	¼ hr.
			(3) Abdominal cramps ++	¼ hr.
			(4) Fatigue +++	¼ hr.
11/16/51	Tapioca	Corn syrup	None	

the patient and myself until all five experiments had been fully recorded. The outcome can be seen in Table I.

It will be noted that tapioca starch pudding caused no discomfort, whether its sweetening agent had been derived from corn or from cane, whereas cornstarch provoked clear-cut and prompt symptoms on both occasions, regardless of the origin of the sweetener. There were very mild, suggestive responses to arrowroot starch (cane sugar was used as its sweetener).

At the finish of these blindfold ingestion studies, the patient was given a large feeding of corn oil (30 c.c.) with no ensuing reaction. The patient's sensitivity to whole corn was not tested by the blindfold ingestion test. She was, however, sensitive to corn on skin test and reported a violent reaction developed when she attempted to eat five kernels of corn.

The conclusion was drawn that the patient was hypersensitive to whole corn (by skin test and history), to cornstarch, and questionably to arrowroot starch, whereas she tolerated full feedings of corn sweetener in the form of syrup when it was included in a tapioca starch pudding. Corn oil was well tolerated. The mild symptoms she reported to have resulted from ingesting corn syrup in the past were probably psychogenic.

It is my general feeling that allergy toward starch is rarely encountered. The infrequency of allergy to cornstarch may very well be due to the manufacturing process which cleans away most of the soluble proteins, minerals, and oil-containing germ centers of the original whole corn. Even after this thorough cleansing process, the starch is further separated by repeated washings and filterings and is left practically free of protein.

In the same manner when one considers how corn syrup is made from this pure cornstarch, it is very conceivable that this further chemical change in the cornstarch may account for the lack of clinical hypersensitivity to corn syrup. Corn syrup is made by pressure cooking an acidified solution of water and cornstarch. In this process, the starch, water, and acid are heated under pressure with steam. A series of chemical reactions thus take place with which the starch is subdivided into the simpler carbohydrates: dextrose, maltose, higher sugars, and dextrins. This latter chemical process probably further diminishes the antigenic property of the original cornstarch to the vanishing point.

The author wishes to thank Dr. Mary Loveless for her cooperation.

REFERENCES

1. Randolph, Theron G., and Yeager, Leona B.: Corn Sugar as an Allergen, Ann. Allergy 7: 651-662, 1949.
2. Bernton, Harry S.: On the Incidence of Sensitiveness to Corn, Ann. Allergy 9: 368-377, 1951.
3. Loveless, Mary H.: Allergy for Corn and Its Derivatives: Experiments With a Masked Ingestion Test for Its Diagnosis, J. ALLERGY 21: 500-509, 1950.

141 EAST 56TH ST.

AN ANTIGEN-ANTIHISTAMINE* MIXTURE FOR THE TREATMENT OF HIGHLY SENSITIVE HAY FEVER PATIENTS

ISADOR RIPPS, M.D., AND ABNER M. FUCHS, M.D., NEW YORK, N. Y.

DURING the past several years, the value of antihistaminic drugs as an adjunct in the treatment of various allergic conditions has become a well-recognized and established fact. In the treatment of hay fever a large variety of these antihistamines has been employed orally or parenterally either for the relief of symptoms or as a supplement in conjunction with various hyposensitization techniques. Arbesman and associates,[1] giving a preliminary oral dose of Pyribenzamine to prevent constitutional reactions in routine hyposensitization treatment, observed that one of the patients could tolerate, without reactions, 50 per cent more allergen than formerly. In the study of a large group of hay fever patients, Fuchs and associates[2] observed that a preliminary oral dose of 50 mg. Pyribenzamine given prior to the injection of pollen antigen permitted these patients to tolerate larger doses of antigen. These patients were able to take a maximum dosage almost twice the amount they usually tolerated when taking the pollen extract alone. Green[3] also observed that he could give larger doses of antigen when 25 mg. Pyribenzamine was administered prior to pollen therapy.

Spearman[4] reported superior results in the treatment of 100 cases of perennial vasomotor rhinitis and seasonal hay fever by injecting an antihistamine intravenously prior to the subcutaneous injection of the specific antigens. Maietta[5] obtained good results in pollinosis by using rapidly increasing hyposensitization doses of pollen antigen made possible by the simultaneous oral administration of suitable antihistaminic drugs over a period of twenty-four hours. Maietta,[6] in a subsequent study, using a combined antigen-antihistaminic technique, was able to shorten the treatment of hay fever and give massive doses of pollen extract with safety. He used Thephorin as the antihistamine, giving 50 mg. doses orally prior to and following the injection of the pollen antigen-aqueous antihistaminic mixture.

It is the purpose of this article to report some clinical observations made when employing a solution of an antihistaminic mixed with pollen extract in the prophylactic treatment of unusually sensitive cases of ragweed pollinosis. We used Decapryn Succinate Minergic Solution, which has proved to be an effective antihistaminic in the treatment of a variety of allergic conditions.[7] Feinberg and Bernstein[8] studied the drug pharmacologically as well as clinically and found it to be highly effective in the inhibition of cutaneous histamine reactions. Sheldon and associates,[9] in a clinical study, found the bene-

From the Department of Medicine, New York University Post-Graduate Medical School, and the Allergy Section, Medical Service, University Hospital.

Received for publication, May 11, 1953.

*Decapryn Succinate Minergic Solution was supplied through the courtesy of the Wm. S. Merrell Company.

ficial effects of Decapryn to be of a similar magnitude to those reported for Benadryl and Pyribenzamine, but of longer duration. Simon,[10] using Decapryn Succinate Minergic Solution mixed with penicillin, was highly successful in reducing the incidence of reactions to penicillin. He also suggested that antihistamines could be easily combined with other preparations to prevent reactions.

PROCEDURE AND TECHNIQUE

The patients selected for this form of therapy comprised a group of 34 adults, who fell into two categories: (a) those who were highly sensitive clinically and by skin test, and (b) those who, in previous years, were unable to undergo satisfactory treatment with the usual aqueous pollen extracts because of repeated marked local or constitutional reactions (Table II). In our clinic all hay fever patients are classified arbitrarily as AA, A, B, or C, depending upon the degree of reaction as determined by intradermal skin tests, using various strengths of aqueous pollen extracts. The patients showing a marked reaction to a solution containing one protein nitrogen unit per milliliter (Cooke and Stull) are classified as AA; those giving a marked reaction to 10 protein nitrogen units are classified as A; to 100 protein nitrogen units as B; and to 500 protein nitrogen units as C. In the group under study, there were 5 patients classified as AA and 29 patients classified as A.

The minergic solution employed in this study contained 5.0 mg. of Decapryn Succinate in each milliliter of a sterile aqueous isotonic solution, preserved with 0.5 per cent chlorobutanol (chloral derivative). One-half milliliter of this solution was mixed with each dose of pollen extract in the same syringe. The injection was prepared by first withdrawing the desired dose of pollen antigen. Following this, 0.5 ml. of the Decapryn Solution was drawn into the same syringe, and the syringe inverted several times to mix the solutions thoroughly. The mixture was then injected subcutaneously in the outer aspect of the upper arm. The injections were given at weekly intervals. No

TABLE I. PROPHYLACTIC TREATMENT
RAGWEED POLLEN EXTRACT IN PROTEIN NITROGEN UNITS*

	WITHOUT DECAPRYN SUCCINATE MINERGIC SOLUTION		WITH DECAPRYN SUCCINATE MINERGIC SOLUTION
INJECTION	CLASS AA UNITS	CLASS A UNITS	CLASS AA AND CLASS A UNITS
1	2	5	25
2	5	10	50
3	10	20	100
4	20	30	200
5	30	40	300
6	40	60	500
7	50	80	700
8	--	100	1,000
9	--	150	1,500
10	--	200	2,000
11	--	300	2,500
12	--	400	3,000
13	--	500	3,500
14	--	---	4,000

*1 unit = 0.00001 mg. protein nitrogen.

other form of antihistamine was administered either orally or parenterally. The usual dosage schedule employed with the aqueous ragweed pollen extracts was not followed. In general, we tried to follow a schedule (Table I) as was successfully employed in our clinic with the use of a slowly absorbing gelatin pollen extract.[11] This schedule was often modified to suit the patient's tolerance for the combined ragweed-antihistamine solution and for the purpose of experimental study.

SKIN SENSITIVITY TESTS

To determine the effect of mixing aqueous ragweed extract and the Decapryn Minergic Solution on the skin response, we performed the following intracutaneous tests on all patients: In the first column we injected a test dose of 95 per cent Decapryn Succinate Minergic Solution. In the second column we injected two test sites with a test dose of aqueous ragweed extract, one containing 10 PN units and the other 100 PN units per milliliter. In the third column we injected three sites with a test dose of the mixed aqueous ragweed extract and a 95 per cent concentration of Decapryn Succinate Minergic Solution. The three combined extracts contained 10 PN units, 100 PN units, and 500 PN units per milliliter, respectively.

The test with Decapryn Succinate Minergic Solution as described above resulted either in a negative or a very slight reaction. The tests with aqueous ragweed extract, 10 and 100 units per milliliter, resulted in a marked and a marked plus reaction, respectively. The tests with the mixtures of aqueous ragweed extracts, 10 and 100 units per milliliter, and 95 per cent Decapryn Minergic Solution resulted in a reduction of the size of the whealing responses to about one-half, and elimination of the zone of erythema. The test with the mixture of aqueous ragweed extract, 500 units per milliliter, and 95 per cent Decapryn Minergic Solution resulted in a moderate reduction of the whealing response and a reduction of the zone of erythema, as well as a lessening of the hazard of a constitutional reaction.

RESULTS

The results of treatment of the 34 adult patients during the seasons of 1951-1952 with the mixed aqueous ragweed extract and Decapryn Succinate Minergic Solution were compared with results obtained following treatment with the regular aqueous ragweed extract during previous years at our clinic, and with results obtained from treatment elsewhere (Table II).

Each patient was individually instructed in the proper manner of evaluating and recording his daily symptoms and reactions. At each clinic visit he was carefully questioned and his report recorded. At the end of the season 20 patients (59 per cent) experienced a satisfactory degree of relief, 13 patients (38 per cent) reported partial relief, and 1 patient (3 per cent) reported no relief. The patients classified as showing a satisfactory degree of relief were those who experienced very slight hay fever symptoms. The patients who experienced at least 50 per cent relief were classified as "partial relief."

TABLE II. RESULTS IN 34 HIGHLY SENSITIVE HAY FEVER PATIENTS TREATED WITH RAGWEED-DECAPRYN SUCCINATE MINERGIC SOLUTION

CASE NO.	CLASS	CEILING DOSAGES RAGWEED-DECAPRYN MIXTURE (UNITS)	CEILING DOSAGES AQUEOUS RAGWEED ALONE (PREVIOUS YEARS)	REACTIONS FROM ANTIHISTAMINIC	REACTIONS FROM POLLEN EXTRACT MIXTURES	RELIEF
1	A	1,500	300	None	Hives and chest heaviness after 1,500 units	Satisfactory
2	A	1,500	150	None	None	Satisfactory
3	A	1,750	---	None	None	Partial
4	A	4,000	1,000	Drowsiness	None	Satisfactory
5	AA	400	---	Drowsiness	Constitutional reactions after 25 and 50 units	Partial
6	A	4,000	1,250	None	None	Satisfactory
7	A	2,500	60	None	None	Satisfactory
8	A	2,000	---	Drowsiness	None	Partial
9	A	1,000	---	None	None	Partial
10	A	2,000	600	None	None	Partial
11	A	2,000	---	Drowsiness	None	Partial
12	A	2,000	70	None	Marked delayed local reaction at 1,500 units	Partial
13	A	1,500	100	Drowsiness	None	Satisfactory
14	A	2,500	200	Drowsiness	None	Satisfactory
15	A	2,500	350	Drowsiness	None	Satisfactory
16	A	1,000	300	None	None	Satisfactory
17	AA	600	10	Drowsiness	Marked local reaction with chest heaviness and wheezing at 600 units	Partial
18	A	1,000	250	None	None	Partial
19	A	2,500	500	Drowsiness	None	Satisfactory
20	A	1,000	---	None	None	Partial
21	A	3,500	---	Drowsiness	None	Satisfactory
22	AA	600	20	None	None	Partial
23	A	1,500	1,000	None	None	Satisfactory
24	A	1,500	50	None	None	Partial
25	AA	2,000	60	None	None	Satisfactory
26	A	1,000	40	None	None	Satisfactory
27	A	1,500	---	None	None	None
28	A	1,000	150	None	None	Satisfactory
29	A	1,250	250	None	None	Satisfactory
30	A	1,500	---	None	None	Satisfactory
31	A	2,500	---	None	None	Satisfactory
32	A	2,000	---	None	None	Satisfactory
33	AA	1,500	---	None	None	Partial
34	A	1,500	---	None	None	Satisfactory

The highest dosages reached with the antigen-antihistamine mixture were many times the ceiling dosages possible with the aqueous ragweed extract alone (Table II). The top dosages were those reached at the onset of the ragweed pollen season. Some of the patients could have tolerated higher dosages of the combined mixture, but no attempt was made to do so because at the onset of the pollen season the dosages were far in excess of the usual top dosages obtained with the regular ragweed extract. Moreover, it was not thought wise to make further increases during the active pollen season. In a few cases, desirable top doses were not reached because of irregular attendance.

SIDE REACTIONS

Ten patients (approximately 29 per cent) complained of slight drowsiness, which usually lasted from fifteen to thirty minutes. This was the only complaint reported. An occasional patient stated that the drowsiness persisted for a few hours. But this side effect could be easily controlled by drinking a cup of black coffee.

LOCAL AND CONSTITUTIONAL REACTIONS

In most instances the immediate local reaction was either negative or very slight. Some patients complained of a slight local burning sensation while the fluid was being injected, but this slightly uncomfortable feeling disappeared within a minute after the needle was withdrawn, and as the treatment progressed they ceased to complain.

Delayed local reactions occurred in less than half the individuals. These reactions appeared a few hours following injections, and were mild to moderate in degree, nondisabling, and lasted from a few hours in the average case to approximately twenty-four to thirty-six hours in the occasional individual. In only two cases was a marked local reaction obtained, one of the delayed type and the other immediate. The marked local delayed reaction resolved spontaneously, without any residual effect. The marked local immediate reaction occurred following a dose of 600 PN units in an AA case, and was accompanied by a moderate constitutional reaction consisting of a sense of heaviness in the chest and wheezing, which persisted for a few minutes. Epinephrine was administered as a countermeasure. In none of the cases did any local residual irritation or induration occur.

Altogether we encountered constitutional reactions in three patients. One was an A case and the other two were AA cases. The reaction in the A case occurred within thirty minutes following a dose of 1,500 PN units and consisted of generalized hives and a sensation of heaviness in the chest. The first AA case, a highly emotional patient, experienced two constitutional reactions following her initial doses. The first reaction occurred within ten minutes of treatment and the second occurred within one hour. The second AA case experiencing a constitutional reaction was the aforementioned patient, who had experienced a marked local reaction. These four constitutional reactions were easily controlled with an injection of 3/10 c.c. of epinephrine (1-1,000) solution, given subcutaneously, and the application of a tourniquet. Considering the type of patient selected for this study, and the fact that these 34 patients made 335 treatment visits, the incidence of constitutional reactions was small (1.2 per cent), as compared with an incidence of 5.3 per cent reported by Schulman and Fuchs[12] when treating 56 hay fever patients of various classes, using regular ragweed extract without an antihistamine.

DISCUSSION

This method of treatment offers interesting possibilities, and has its chief value in the management of selected, highly sensitive pollen cases, where treatment with regular aqueous pollen extract has been difficult.

The injection of the mixture of aqueous ragweed extract and Decapryn Succinate Minergic Solution has permitted these patients to tolerate ceiling dosages in excess of those reached with the regular aqueous extracts. Moreover, it was possible to give greater dosage increases. All but one patient treated by this method stated that the relief obtained was the most satisfactory since the onset of their hay fever. In most patients the combined pollen-antihistaminic solution was effective in the prevention of immediate local reactions. In the other patients, the local reactions were minimized. This permitted the patients to receive their injections with greater comfort.

Severe local reactions were inhibited in nearly all patients, and constitutional reactions, although not entirely eliminated, were relatively infrequent. This form of therapy permits the treatment of highly sensitive patients, who are prone to local and constitutional reactions, with relative safety, using more rapidly increased and higher doses. Hyposensitization treatment is therefore made more acceptable to these patients and becomes a lesser problem to the physician. Because of the apparent increased safety of treatment which this method offers, we have considered the feasibility of increasing the time interval between treatments. Some patients, who were compelled to miss a week or two between treatments, were able to take the same previous dose, or even an increase in dose, without untoward effects. In no instance was it necessary to diminish the dose except following a constitutional reaction. This fact suggests the possibility of putting these highly sensitive patients on a monthly basis of treatment, which has not been possible heretofore, when using the ordinary aqueous pollen extracts.

The results obtained with the combined ragweed-Decapryn Succinate Minergic Solution in the treatment of highly sensitive hay fever patients were comparable to the results previously reported when slowly absorbed gelatin pollen extracts were employed.[11]

The disadvantages incident to the use of combined antigen antihistamine mixture are the inconvenience of preparing it before administration when the patient is obliged to continue his hay fever treatment elsewhere and the possibility of a delayed constitutional effect occurring several hours after the injection when the patient is no longer under the observation of the physician. The threat of a constitutional reaction, which is ever-present, regardless of the form of pollen therapy, has not been eliminated by this procedure, but would seem to be minimized.

SUMMARY

1. Thirty-four highly sensitive hay fever patients were treated preseasonally with combined ragweed-Decapryn Succinate Minergic Solution.

2. A greater tolerance for this combined mixture was noted. Higher ceiling dosages and greater dosage increases were given with safety.

3. Local and constitutional reactions were infrequent and easily controlled.

4. More effective clinical relief was obtained.

5. The chief value of the combined ragweed-Decapryn Succinate Minergic Solution is in the therapy of hay fever patients so sensitive that they cannot be treated satisfactorily with the usual aqueous pollen extracts.

REFERENCES

1. Arbesman, C. E., Koepf, G. F., and Lenzner, A. R.: Clinical Studies With N'pyridyl, N'benzyl, Dimethylethylene-Diamine Monohydrochloride (Pyribenzamine), J. ALLERGY **17**: 275-283, 1946.
2. Fuchs, A. M., Schulman, P. M., and Strauss, M. B.: Clinical Studies With Pyribenzamine in Hay Fever, J. ALLERGY **18**: 385-390, 1947.
3. Green, M. A.: Letters, Internat. Correspondence Soc. Allergists **10**: 100, 1947.
4. Spearman, G. K.: Treatment of Hay Fever by an Intravenous Antihistamine, Ann. Allergy **10**: 192-193, 1952.
5. Maietta, A. L.: Unusually Good Results in Pollinosis With Combined Antigen-Antihistamine Therapy. Shortening the Treatment of Hayfever. Study I, Ann. Allergy **7**: 789-798, 1949.
6. Maietta, A. L.: Shortening the Treatment of Hayfever. The Combined Antigen-Antihistamine Technique in Pollen Therapy. Study III, Ann. Allergy **8**: 645-648, 1950.
7. Brown, E. A., Weiss, L. R., and Maher, J. P.: The Clinical Evaluation of a New Histamine Antagonist "Decapryn," Ann. Allergy **6**: 1-6, 1948.
8. Feinberg, S. M., and Bernstein, T. B.: Histamine Antagonists. X. A New Antihistaminic drug, 2-[α-(2-Dimethylaminoethoxy)-α-Methyl-Benzyl]-Pyridine Succinate (Decapryn Succinate); Experimental and Clinical Results, J. Lab. & Clin. Med. **33**: 319-324, 1948.
9. Sheldon, J. M., Weller, K. E., Haley, R. R., and Fulton, J. K.: Clinical Observations With Decapryn, a New Antihistaminic Compound, Univ. Michigan Hosp. Bull. **14**: 13-15, 1949.
10. Simon, S. W.: Hypo-Allergic Penicillin, Ann. Allergy **8**: 194-201, and 289, 1950.
11. Spain, W. C., Fuchs, A. M., and Strauss, M. B.: A Slowly Absorbed Gelatin-Pollen Extract for the Treatment of Hay Fever, J. ALLERGY **12**: 365-377, 1941.
12. Schulman, P. M., and Fuchs, A. M.: Clinical Studies With Iron as Adjunct to Pollen Immunization and Antihistaminic Therapy in Hay Fever, J. ALLERGY **20**: 444, 1949.

THE USE OF PRANTAL IN ASTHMA: A SPIROMETRIC EVALUATION

SIDNEY DANN, M.D., FREDERICK R. BROWN, M.D., AND
HERBERT S. KUPPERMAN, M.D., PH.D., NEW YORK, N. Y.

THE use of anticholinergic substances for the treatment of bronchial asthma has a long historic tradition in the therapeutics of this condition. Many observers in the past have considered bronchial asthma to be the result of an imbalance in the autonomic nervous system. Among the earliest observers in this field were Eppinger and Hess[4] who included asthma in their theory of vagotonia as an example of "pathologic vagotonia." Proceeding on this basis, atropine and many atropine-like drugs have been tested in the past for the treatment of asthma. Clinically, however, the use of these drugs, notably atropine, has been very disappointing, although some workers still cling to their use in some cases. Many writers and practically all the standard textbooks[1, 5, 6] on the subjects warn against the use of this drug. They comment upon its effect in "drying out the secretions" and "inspissating" the mucous plugs in the bronchi. They have pointed out that despite evident bronchodilating qualities in the experimental animal or in the isolated lung preparation, clinically atropine has often led to dangerous complications and even, in some instances, to death.

Beakey and his co-workers[2] have made some interesting comments in this respect: "The wet, sweating, hypotensive asthmatic patient who may be exhibiting a systemic picture of para-sympathetic stimulation (pathological vagotonia) is almost completely resistant to ordinary methods of treatment. It is possible that hyoscine, hyoscyamine, or a derivative may exhibit sufficient sedation, as well as broncho-spasmolytic properties, that its use might be indicated in spite of its drying action. It is hoped that the pharmacologist will be able to provide a compound retaining the sedative action and the usual anti-cholinergic properties of the parent drug, but with less local effect on the bronchial mucosa." With this in view it was thought of interest to evaluate Prantal Methylsulfate (di-phenethinylmethyl sulfate), a new synthetic anticholinergic compound, in the treatment of asthma. This drug has recently been introduced as an anticholinergic agent for the management of peptic ulcer and other conditions characterized by gastrointestinal hypertonicity and gastric hyperacidity. Our experiences with this drug are reported in this paper.

METHOD

A spirometric technique was employed in the evaluation of this preparation. This technique has been described elsewhere.[3] Briefly it employs a battery of breathing tests consisting of the vital capacity following a normal expiration, the vital capacity following a deep expiration, and the maximal breathing capacity. The last is performed in two variations.

From the Department of Therapeutics, New York University-Bellevue Medical Center, and the Allergy Clinic, Third Division, Bellevue Hospital.

Received for publication, May 11, 1953.

The first method is called the deep breathing type of maximal breathing capacity, hereafter to be called the deep M.B.C. In this test the patient breathes as deeply and rapidly as possible. The second type is the rapid maximal breathing capacity, hereafter to be called the rapid M.B.C. This is carried out with the patient breathing as rapidly as he can without regard to depth.

For purposes of simplicity we utilized only one vital capacity in our calculations, namely, that following a normal expiration. Patients were seen early in the morning following their usual breakfast. The only restrictions imposed were on the use of tobacco during the test period and the administration of any medications on the day of testing. After an adequate rest period following arrival in the laboratory, the testing procedure commenced with the premedication battery of tests repeated as necessary until it was apparent that the patient was making the maximal effort.

In our most recent studies we ran a second control period one-half hour following the first series of test runs to insure ruling out factors such as the effect of rest, spontaneous improvement upon coming indoors from a cold environment, the learning element, variation in voluntary effort, etc. Following an adequate control period, the patient was given the medication to be tested, in this case Prantal, either orally or intramuscularly. The same battery of tests was thereafter repeated at half-hourly intervals under identical conditions; this usually extended over a two-hour period.

The machine used in this study was the Collins respirometer which is basically a Benedict-Roth water-seal apparatus which has the additional advantages of a nine-liter tank and a two-speed kymograph. The former feature reduces the oxygen dilution factor. The latter increases the legibility and the ease of calculation of the tracing, especially in the rapid M.B.C. studies.

At the time of testing, patients were classified in one of three categories: *Class I* included those patients who showed no physical evidence of asthma or auscultation of the chest and who were entirely free of symptoms as determined by careful questioning. *Class III* asthmatics were those who were tested during the course of an acute episode. These were the patients who under ordinary circumstances would seek attention at the clinic or doctor's office or who would administer injections themselves. *Class II* patients were those who were experiencing "mild" asthmatic difficulty. These were the patients who upon auscultation showed the typical wheezing or who complained of respiratory discomfort in the absence of physical signs. These patients had what would be called clinically a moderate degree of asthma, and on questioning they usually stated that this was their "ordinary" condition.

Using the previously described technique and method of patient classification, we have carried out spirometric studies on twenty-four patients* for a total of twenty-eight separate test periods, four patients being tested on two separate occasions. The results of these studies are presented in Table I. As

*These patients were in attendance at the Allergy Clinic, Third Division, Bellevue Hospital.

TABLE I. SPIROMETRIC STUDIES ON

NO.	PATIENT	AGE	SEX	CLASS OF ASTHMA	VITAL CAPACITY			GRADE OF IM-PROVE.	MAXIMAL BREATHING CAPACITY (DEEP)			PRANTAL
					INITIAL (C.C.)	MAXIMAL (C.C.)	% CHANGE		INITIAL (L./MIN.)	MAXIMAL (L./MIN.)	% CHANGE	GRADE OF IM-PROVE.
1	G. B.	70	M	II	2900	3100	6.7	0	57.6	85.8	48.8	1
2	E. K.	69	F	II	2200	2400	2.5	0	30.4	48.0	59.0	2
3	S. B.	63	F	II	1450	2000	38.0	1	36.8	49.3	32.0	1
4	S. B.	50	F	I	1850	2500	35.0	1	40.0	52.8	32.0	1
5	R. C.	30	F	II	1550	1700	9.6	0	32.0	45.6	42.5	1
6	M. F.	63	F	II	2000	2300	15.0	0	62.4	62.4	0.0	0
7	A. F.	46	F	I	2500	2800	12.0	0	73.6	90.0	22.0	1
8	R. F.	40	M	II	3000	4200	40.0	1	28.8	82.6	190.0	4
9	G. F.	51	F	II	2550	3100	22.0	1	67.2	118.4	76.1	2
10	R. H.	61	F	II	2200	2500	13.8	0	25.6	31.2	22.7	1
11	S. K.	56	F	II	2000	3000	34.0	1	57.6	74.0	28.0	1
12	G. K.	70	M	II	2400	3050	27.0	1	66.0	74.8	13.1	0
*13	G. K.	70	M	II	3000	3100	3.0	0	72.8	84.0	16.5	0
14	H. M.	36	F	I	2400	2950	23.0	1	72.0	100.8	40.0	1
15	L. O.	52	F	II	1300	1700	31.0	1	40.0	48.8	22.0	0
16	A. O.	32	F	III	2000	2200	10.0	0	31.2	36.4	16.3	0
17	A. R.	31	M	III	3900	5200	33.3	1	49.4	64.6	30.9	1
*18	A. R.	31	M	III	4100	5950	45.0	1	67.0	92.4	37.5	1
19	J. R.	51	M	I	5350	6000	12.2	0	74.4	89.6	17.0	0
20	C. S.	53	M	I	3700	4250	11.5	0	67.2	103.2	53.0	2
21	L. S.	63	M	II	3000	3900	30.0	1	24.0	39.2	62.5	2
22	A. S.	67	M	II	3500	4400	25.0	1	22.0	46.4	110.0	4
*23	A. S.	67	M	III	2650	4400	66.6	2	21.0	52.8	151.0	4
24	A. Sh.	63	M	III	3300	4000	21.0	1	50.4	69.6	38.0	1
25	I. S.	37	M	III	3600	5400	50.0	1	38.4	118.4	208.0	4
26	J. W.	29	M	I	5250	5400	3.0	0	156.0	170.0	9.0	0
*27	J. W.	29	M	II	3700	4200	13.5	0	96.8	104.0	7.5	0
28	L. T.	46	F	II	3100	3650	17.8	0	73.8	84.8	15.3	0

would be expected, most of the patients when seen in their untreated state fell into Class II. They are all well known to us and had been studied on several occasions previously for similar spirometric studies carried out in the evaluation of other drugs. They can be considered as trained subjects, although, as pointed out in previous papers, the training element in this type of study is on the whole slight. The age distribution varied from 29 to 70 years. The tests were carried out on fifteen male and thirteen female patients.

The therapeutic responses graded from 0 to 4 were judged by the changes in the vital capacity and both types of maximal breathing capacity tests over the control readings. The results are recorded in Table I. It has been our experience in previous studies in which the basic criteria for spirometric evaluation were determined that any change under 20 per cent in the three basic spirometric evaluations could be considered within the range experimental error and to be thought of as evidence of significant therapeutic effectiveness. Most asthmatics tested after injections of saline solution gave variations of less than 10 per cent, but a few ranged just below 20 per cent

PRANTAL (25 MG. INTRAMUSCULARLY)

GRADE OF IMPROVE.	MAXIMAL BREATHING CAPACITY (RAPID) INITIAL (L./MIN.)	MAXIMAL (L./MIN.)	% CHANGE	GRADE OF IMPROVE.	SUBJECTIVE RESPONSE	TOXICITY
1	50.4	70.4	40.0	1	Slightly improved	None
2	41.6	41.6	0.0	0	Improved	Mouth dry
1	33.6	46.0	37.0	1	"Better," less wheezing	Throat dry, drank several glasses water during test period
1	39.6	62.4	57.0	2	Better	Throat dry and tickled, slight chest pain
1	39.2	56.0	42.0	1	None	Throat pasty
0	64.0	68.4	7.0	0	Better	Throat dry
1	64.0	86.4	35.0	1	"Breathing better"	Mouth dry, slight dizziness, cramps
4	59.2	67.2	20.2	1	Better	None
2	56.0	83.2	48.5	1	Better	None
1	38.8	38.8	0.0	0	None	"Dry," drank large quantities of water
1	48.0	57.6	20.0	1	None	Slightly dry
0	47.6	100.8	110.0	4	Considerably improved	Slightly dry
0	80.0	84.0	5.0	0	Improved	Dry
1	10.0	112.0	12.0	0	Better	"Pins and needles" sensation, headache, blurred vision
0	50.4	52.0	3.2	0	None	Slightly dry
0	36.0	36.0	0.0	0	Improved	Extremely dry
1	47.6	72.0	51.2	1	Improved, "best drug ever taken"	Dry
1	36.8	76.0	106.0	4	Very good	Dry
0	70.0	75.0	7.0	0	Thinks he's better	Dry
2	72.0	98.8	36.0	1	None	None
2	29.4	42.0	46.0	1	Improved	Mouth dry
4	27.0	44.0	63.0	2	Very good	Slightly dizzy
4	30.0	46.8	51.0	2	Excellent	None
1	52.8	64.4	22.0	1	Much improved	None
4	28.0	67.6	71.0	2	Better	"Dry"
0	93.6	114.4	22.0	1	None	None
0	67.2	72.0	7.4	0	None	None
0	65.0	95.6	44.0	1	"Helped"	None

Key to grade of response:
0 = 0 to 20 per cent
1 = 21 to 50 per cent
2 = 51 to 75 per cent
3 = 76 to 100 per cent
4 = 101 +
*Tests repeated on a different day.

which has therefore been designated as the upper limit of experimental variation in this report. Table II shows the range of response noted when twenty-eight patients received 25 mg. of Prantal intramuscularly.

TABLE II. THERAPEUTIC RESPONSE OF ASTHMA TO PRANTAL (25 MG. INTRAMUSCULARLY)

GRADE	VITAL CAPACITY NO. PATIENTS	VITAL CAPACITY % CASES	MAXIMAL (DEEP) BREATHING NO. PATIENTS	MAXIMAL (DEEP) BREATHING % CASES	MAXIMAL (RAPID) BREATHING NO. PATIENTS	MAXIMAL (RAPID) BREATHING % CASES
0	13	46.4	9	32.2	9	32.2
1	14	50.0	11	39.2	13	46.4
2	1	3.6	4	14.3	4	14.3
3	0	0.0	0	0.0	0	0.0
4	0	0.0	4	14.3	2	7.1

TABLE III. PER CENT DISTRIBUTION OF LEVELS OF THERAPEUTIC RESPONSE OF FUNCTIONS TESTED

FUNCTION TEST	AMINOPHYLLINE 0.25 GM. IV		AMINOPHYLLINE 0.5 GM. IV		EPHEDRINE SULFATE 25 MG. IM		EPHEDRINE SULFATE 50 MG. IM		EPINEPHRINE 0.25 MG. IM		EPINEPHRINE 0.5 MG. IM		PRANTAL METHYLSULFATE, 25 MG. IM.	
	NO. OF PATIENTS	% CASES	NO. OF PATIENTS	% CASES	NO. OF PATIENTS	% CASES	NO. OF PATIENTS	% CASES	NO. OF PATIENTS	% CASES	NO. OF PATIENTS	% CASES	NO. OF PATIENTS	% CASES
Vital capacity:														
Grade 0	18	66.6	19	59.3	26	96.3	16	61.5	16	72.7	8	40.0	13	46.4
Grade 1	7	25.9	7	21.9	1	3.7	10	39.5	5	22.7	9	45.0	14	50.0
Grade 2	1	3.7	3	9.4					1	4.6	2	10.0	1	3.6
Grade 3	1	3.7	3	9.4							1	5.0		
Grade 4														
Maximal (deep) breathing:														
Grade 0	10	37.0	9	31.0	18	69.2	11	42.3	6	27.2	3	15.0	9	32.2
Grade 1	11	40.7	15	51.7	7	26.1	8	29.2	12	54.4	11	55.0	11	39.2
Grade 2	5	18.5	4	13.8	1	4.7	6	23.3	1	4.5	1	5.0	4	14.3
Grade 3	1	3.8	1	3.5			1	5.2	2	9.4	2	10.0		
Grade 4									1	4.5	3	15.0	4	14.3
Maximal (rapid) breathing:														
Grade 0	9	33.3	9	31.0	18	69.2	8	32.0	8	36.3	5	25.0	9	32.2
Grade 1	11	40.7	15	51.7	5	19.2	11	44.0	9	40.9	7	35.0	13	46.4
Grade 2	2	7.4	4	13.8	1	3.6	6	24.0	1	4.5	4	20.0	4	14.3
Grade 3	4	14.8	1	3.5	2	8.0					3	15.0		
Grade 4	1	3.8							4	18.3	1	6.0	2	7.1

Key to grade of response:

0 = 0 to 20 per cent. No response.
1 = 21 to 50 per cent.
2 = 51 to 75 per cent.
3 = 76 to 100 per cent.
4 = 101 + per cent.

We have previously collected spirometric data on a large number of asthmatic patients using three of the standard drugs most commonly prescribed in the treatment of bronchial asthma. Thus, the therapeutic effects of two dose levels, each of epinephrine, ephedrine, and aminophylline, were observed. The first two drugs were administered intramuscularly and the third intravenously. Each dose level was tested on approximately thirty patients distributed in the three classes of severity of asthma. An over-all compilation of the results is listed in Table III. These data serve as a standard basis of comparison in evaluating the effectiveness of other drugs introduced for the treatment of bronchial asthma. The last column of this table includes corresponding figures obtained in the present spirometric study on Prantal. These data indicate that the response to parenteral Prantal is inferior only to that obtained following the intramuscular administration of 0.5 mg. of epinephrine. Prantal proved to be as effective as both dose levels of aminophylline and 0.25 mg. of epinephrine, and superior to ephedrine in the two dose levels.

Data on the spirometric evaluation of Prantal after oral administration of 50 mg. are presented in Table IV. It is noted that in the nine patients studied, the therapeutic response was minimal. No side effects, however, were experienced by any one of the nine patients, as contrasted with the large number of side effects reported by the group of patients to whom the drug was administered parenterally.

TABLE IV. PRANTAL 50 MG. (ORALLY) IN ASTHMA

PATIENT	SEX	AGE	CLASS OF ASTHMA	CHANGE IN VITAL CAPACITY	CHANGE IN MAXIMAL BREATHING CAPACITY	SIDE EFFECTS	SUBJECTIVE RESPONSE
R. S.	M	55	II	+26.0 (1)*	+4.0 (0)*	0	"Slightly better"
R. S.	M	55	II	+20.0 (1)	+18.0 (0)	0	Feels "clearer" with some relief of congestion
W. A.	M	62	III	0.0 (0)	+14.0 (0)	0	No change
J. R.	M	51	II	2.4 (0)	-22.0 (0)	0	No change
R. W.	M	54	III	4.9 (0)	8.8 (0)	0	Feels "better"
D. B.	F	49	III	-8.0 (0)	+16.0 (0)	0	Worse
A. S.	M	67	II	+3.0 (0)	-8.0 (0)	0	"Some help," but only for short periods. No relief by end of testing period
J. R.	M	72	I	+1.0 (0)	+22.0 (1)	0	No change
W. R.	F	35	II	-7.0 (0)	+14.0 (0)	0	"Much improved." However, still wheezing audibly

SUMMARY

Grade of Improvement	0	1	2	3	4	5	Per Cent Improved
Vital capacity	7	2	0	0	0	0	22.2
Maximal breathing capacity	8	1	0	0	0	0	11.1

Key:
(0) 0 to 20 per cent.
(1) 21 to 55 per cent.
(2) 51 to 75 per cent.
(3) 76 to 100 per cent.
(4) 101 + per cent.

Six patients were studied spirometrically following the combined oral administration of 50 mg. of Prantal and 4 mg. of Chlor-Trimeton. The results are listed in Table V. Again, the therapeutic responses seem to be of a very moderate nature. Six patients were studied after the oral use of 4 mg. of

TABLE V. SPIROMETRIC STUDIES ON PRANTAL AND CHLOR-TRIMETON (ORALLY)

PATIENT	AGE	SEX	CLASS OF ASTHMA	DRUG*	VITAL CAPACITY % CHANGE	VITAL CAPACITY †GRADE OF IMPROVE.	MAXIMAL BREATHING (DEEP) % CHANGE	MAXIMAL BREATHING (DEEP) †GRADE OF IMPROVE.	MAXIMAL BREATHING (RAPID) % CHANGE	MAXIMAL BREATHING (RAPID) †GRADE OF IMPROVE.	SUBJECTIVE RESPONSE	TOXICITY
L. S.	53	M	II	Prantal and Chlor-Trimeton	0.0	0	+38.0	1	0.0	0	Moderately relieved Better than ephedrine	None
W. A.	62	M	II	Prantal and Chlor-Trimeton	9.0	0	+26.0	1	50.0	1	No help. "I expected an injection	None
S. B.	50	F	II	Prantal and Chlor-Trimeton	2.0	0	5.0	0	0.0	0	Slightly relieved	None
O. D.	13	F	II	Prantal and Chlor-Trimeton	0.0	0	30.0	1	0.0	0	"Breathing easier"	None
S. S.	42	F	II	Prantal and Chlor-Trimeton	2.0	0	42.0	1	0.0	0	"Feels slightly better"	None
A. W.	14	F	I	Prantal and Chlor-Trimeton	4.0	0	0.0	0	0.0	0	No change	None
Total						0	66.6 (All Grade I)		16.6 (Grade I)			0
A. G.	35	F	II	Chlor-Trimeton	3.0	0	9.6	0	14.0	0	No change	None
M. G.	68	M	II	Chlor-Trimeton	0.0	0	12.0	0	0.0	0	"Cleared slightly"	None
G. F.	50	F	II	Chlor-Trimeton	2.8	0	4.0	0	0.0	0	"Chest slightly better"	None
M. C.	22	F	II	Chlor-Trimeton	0.0	0	3.0	0	6.8	0	"Slightly better"	None
J. C.	55	F	II	Chlor-Trimeton	11.1	0	62.0	2	26.0	0	Chest clearer	None
S. M.	62	M	II	Chlor-Trimeton	0.0	0	8.0	0	8.0	0	No change	None
Total						0	16.6 (Grade II)		16.6 (Grade I)			0

*Prantal 50 mg.; Chlor-Trimeton 4 mg.

†*Key to grade of improvement:*

0 = 0 to 20 per cent.

1 = 21 to 50 per cent.

2 = 51 to 75 per cent.

Chlor-Trimeton alone. Responses here, too, were of a very minor degree (Table V). When Prantal is given orally in 50 mg. doses, we feel that such a preparation is devoid of any significant therapeutic benefit. It was our feeling at the time that the slight degree of improvement in a few of the cases might well be attributed to minor spontaneous remissions occasionally noted during the course of the study.

The increased percentage of response in maximal breathing capacity when the drugs were used in combination orally as compared to the use of Chlor-Trimeton or Prantal alone might suggest some degree of synergism. Such a conclusion, however, is not entirely warranted since the series were small. Furthermore, all the responses, except in one instance, were relatively slight and in the first level of therapeutic effect. A minor shift in spirometric readings in a few instances could have markedly altered the results.

DISCUSSION

The spirometric evaluation of 25 mg. Prantal given intramuscularly to asthmatics indicates that this drug produces satisfactory responses in a large percentage of the cases. In a recent paper Vickers[7] has summarized his experiences with Prantal administered intramuscularly in doses ranging from 10 to 15 mg. Twenty patients, all suffering from acute asthmatic attacks, received injections and were relieved in two to five minutes. The effects were often described as "dramatic" by the patients and were considered to be the equivalent of any other therapy received previously. The results in a few cases of status asthmaticus ranged from transient, mild relief to complete absence of therapeutic effect. A few patients complained of mild dryness of the mouth. It is noted that the doses were smaller than the one used in our series. No spirometric measurements were carried out in the group.

It is of interest to note that our previous experiences with this drug when tested orally were very disappointing. A 50 mg. dose given by mouth proved to be almost completely ineffectual. The lack of oral effectiveness of Prantal as contrasted with excellent response to intramuscular administration would imply that Prantal is either poorly absorbed orally or inactivated more efficiently by the oral route. Further evidence of probable poor absorption is evidenced by the lack of toxicity when the patient was given the drug by mouth as contrasted with the high percentage of side reactions when the drug was given intramuscularly (Table I). These untoward effects were characterized primarily by atropine-like side effects, namely, dryness of the mouth and throat. Other side reactions included mild dizziness, "pins and needles" sensation, headache, and mild blurring of vision. No significant degree of mydriasis was noted in this series, although careful measurements were not carried out in these experiments. Toxicity in most cases, however, was extremely mild and in some instances was elicited only after careful questioning of the patients.

It is evident that at the dose level employed these effects could not be considered as a significant deterrent to the use of the drug. No significant

gastrointestinal complaints, which are occasionally associated with excess dosage of anticholinergic drugs, were noted in this series. It is possible that by increasing the oral dose one may be more successful in treating the asthmatic with Prantal and this may obviate the necessity for its parenteral use. Probably in some instances the effective oral dose will be within the range producing minimal side effects, such as dryness of the mouth. However, it may be that in oral usage a more careful calibration of the dosage may be possible in which maximal therapeutic response and minimal to absent side reactions may be obtained. It is suggested that in further attempts at oral use the dosage be started at 100 mg. given every four to six hours and be increased to the point of tolerance in the effort to obtain maximal therapeutic response. Clinical studies are being carried out at the present time to determine that dosage. It is our experience that the side effects of Prantal are less distressing to the patient than are those associated with comparable doses of epinephrine and ephedrine. Special caution, however, is indicated, particularly in the older age group where an increased potentiality for glaucoma is present.

The subjective responses to this drug are noted in Table I. Again, it is seen that a large majority of the patients testified to a satisfactory effect. However, we would consider this the least important result of the study since the spirometric studies themselves have been devised in an effort to rule out the subjective elements in evaluating response to bronchodilating agents. Our experiences in the past with distilled water administered to asthmatics intramuscularly showed a fairly large percentage of excellent therapeutic response subjectively when spirometric studies revealed the expected total lack of improvement.

It is possible that Prantal may satisfy some of the pharmacologic criteria suggested by Beakey[2] and his group as discussed previously. The effect of this preparation suggests further that the use of anticholinergic drugs basically possesses considerable merit in the treatment of bronchial asthma. A further study of such compounds in the treatment of this disease is indicated. It is possible that synthesis of other anticholinergic substances may, in the future, provide drugs which will have a more specific effect upon the bronchial mucosa, while at the same time minimizing or reducing the toxic and unpleasant side effects associated with anticholinergic compounds at the time. It is realized, of course, that no basic conclusions regarding the mechanism or etiology of asthma, particularly with reference to chemical mediation, can be drawn from this study.

CONCLUSIONS

1. The spirometric study of Prantal administered intramuscularly in 25 mg. doses to twenty-four patients undergoing twenty-eight trials indicates that this drug has considerable potency as a bronchodilating agent.

2. The drug at this dose proved to be equal in effectiveness to 500 mg. of aminophylline, intravenously, or 0.25 mg. of epinephrine, intramuscularly.

Twenty-five milligrams of Prantal (intramuscularly) was somewhat inferior to 0.5 mg. of epinephrine but superior to 50 mg. of ephedrine, both administered intramuscularly.

3. Failure of response to a 50 mg. dose administered orally would indicate that the drug is poorly absorbed or inactivated more efficiently by this route so that adequate bronchodilating activity is not achieved at this dose level.

4. The side effects in most instances in this series were minimal and of no great clinical importance. However, eye and gastrointestinal complaints were noted in this series and should be sought for carefully when giving high dosage levels.

Appreciation is expressed to Dr. Norman Heminway of the Division of Clinical Research of the Schering Corporation for the generous supplies of Prantal and Chlor-Trimeton used in this study.

REFERENCES

1. Abramson, Harold A., Editor: Treatment of Asthma, Baltimore, 1951, Williams & Wilkins Company.
2. Beakey, John F., Bresnick, Elliott, Levinson, Leon, and Segal, Maurice S.: Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm, III. Anticholinergic Agents, Ann. Allergy **7**: 113, 1947.
3. Dann, S., and Batterman, R. C.: Technique for the Screening in Man of Bronchodilating Drugs, Federation Proc. **9**: 267, 1950.
4. Eppinger, H., and Hess, L.: On the Pathology of the Vegetative Nervous System, Ztschr. f. klin. Med. **67**: 345, 1909; **68**: 205, 1909.
5. Tuft, Louis: Clinical Allergy, Philadelphia, 1937, W. B. Saunders Company.
6. Urbach, Erich, and Gottlieb, Philip M.: Allergy, ed. 2, New York, 1946, Grune & Stratton, Inc.
7. Vickers, Martyn A.: Clinical Trial of Prantal Methylsulfate in Acute Asthmatic Attacks. Preliminary Report, J. Maine M. A. **43**: 381-2, 1952.

ANAPHYLACTIC SHOCK FOLLOWING PENICILLIN THERAPY IN BRONCHIAL ASTHMA

ALEXANDER STERLING, M.D.,* PHILADELPHIA, PA.

A GREAT deal has been written about the morbidity and mortality following injections of penicillin.[1, 2] Penicillin reactions may be local or generalized; may produce pruritus, urticaria, exfoliative dermatitis, angioneurotic edema, or anaphylactic shock which occurs immediately, while the urticaria and angioneurotic edema may be delayed for a week or longer.

We will discuss here the surprise alarm reactions (anaphylactic shock), the possibility of which many forget unless they have had the personal experience of witnessing a patient near death within minutes after an injection.

It is doubtful if anaphylactic shock to penicillin, whether crystalline, potassium, aqueous, procaine, etc., ever occurs at the first injection. Sensitization may take place from previous oral use, or when repeated injections have to be given daily for prolonged periods. We will assume that sensitivity to procaine or other vehicles has been eliminated. Daily injections of 300,000 units of penicillin given for one or two weeks are commonly used in chronic respiratory infection. We use this treatment freely in asthmatic bronchitis when the patients have accompanying mucopurulent expectoration, no matter what the original specific factor.[3] Frequently we have used it for two-week periods, three or four times during the winter months with excellent results. The physician should never hesitate to use it when indicated.

Considering the amount of penicillin used, anaphylactic shock reactions are extremely uncommon. But because of the severity when they do occur, we have found certain precautions necessary.

In checking the medical literature[5-10] we found only one article in which signs and symptoms have been pointed out to the physician which he could use to guide him against the possible occurrence of anaphylactic shock. Quoting from Waldbott's article in the *Journal of the American Medical Association* (1949)[6]: "It was noted that this patient had severe urticaria, some aggravation of asthma, joint pains and slight fever . . . about one week after the last administration of penicillin. This had not been identified at the time as serum sickness from penicillin, but in all probability presented the outward signs of the development of sensitization to penicillin."

All nine of our patients who had shock reactions (three of them almost fatal) noticed some symptoms after the one or two preceding injections of penicillin but did not consider them severe enough to mention.

It is our suggestion to note carefully reactions after the previous injection of penicillin. If any one or all of the five cardinal symptoms appear, in ad-

Received for publication June 17, 1953.

*Chief, Department of Allergy, Eastern Division, Albert Einstein Medical Center.

dition to aggravation of existing chest condition, we can be forewarned of anaphylactic shock and refuse further parenteral penicillin therapy. We can be guided by the following symptoms:

1. Syncope, mild to severe, at the time of injection, or a feeling of faintness recurring periodically for the following three to four hours.

2. Sensation of burning or heat throughout the body, especially in the throat, palms of hands, soles of feet (similar to reaction after intravenous calcium).

3. Local or generalized pruritus *never before present* may occur in various parts of the body, beginning within a few hours after the injection.

4. Choking sensation in the throat, with increasing cough, dyspnea, and wheezing.

5. Severe paroxysmal pain varying in location, such as precordial, epigastric, or diaphragmatic.

The number of injections needed to sensitize an individual varied considerably in our nine cases:

One was sensitized after 12 injections
Two were sensitized after 18 injections
Four were sensitized after 26 injections
Two were sensitized after 54 injections

Penicillin G or procaine penicillin was used for all. Intervals between penicillin series varied from two weeks to six months. None of our reactions occurred at a first injection of any series.

(a) An effort was made to skin test patients suspected of penicillin sensitivity before giving injections, but it proved an unreliable guide. We had ten patients who gave false-positive skin tests, that is, the skin test was positive but there was no reaction after injection. We have not observed negative skin tests which have been followed by reactions to subsequent injections.

(b) The occurrence of angioneurotic edema of the uvula after using penicillin powder by inhalation is not a contraindication to using penicillin by intramuscular injection. Three of our patients who had such reactions after penicillin inhalation later received intramuscular penicillin with full therapeutic benefit and no shock reaction.

(c) When we found that existing dermatitis in patients with dermatophytosis and varicosities of the legs were much more pronounced after penicillin injection, we hesitated at first to use it again. However, subsequent injections in these individuals produced no other reaction except the previously mentioned local discomfort.

None of these three tests were conclusive guides to penicillin sensitivity and we had to rely on our five cardinal symptoms.

Since then all patients were instructed to wait in the office fifteen minutes after each injection and to report any untoward signs or symptoms occurring

immediately following the last injection. Fifteen patients who experienced one or more of the suggested symptoms were refused further injections of penicillin. A trial injection was made in three suspicious cases to determine whether we were justified in withholding the penicillin injections and, to our regret, we caused three anaphylactic shock reactions. One patient, who did not believe his reaction was due to penicillin, insisted on another trial. He had as severe a reaction within two minutes after receiving 30,000 units as he had the week before after 300,000 units of penicillin.

In the emergency of a shock reaction the greatest immediate aid is obtained with small doses, 2 to 3 minims (0.12 to 0.2 ml.), of epinephrine solution (1:1,000), given intradermally every two minutes until the patient is out of danger, usually fifteen or twenty minutes, or beyond help. In many of the fatal shock reactions to penicillin reported to date,[5-9] aminophylline or antihistaminics were used. Epinephrine directly in the heart muscle has been used when the patient was almost moribund. Remember that large doses of epinephrine are sometimes dangerous in themselves.[11] In one instance death followed after an injection of penicillin was given at home by a member of the family, where epinephrine or other emergency treatment was not available. This episode should serve as warning to make sure that penicillin trays at home, office, or at hospital always have a sterile syringe and epinephrine ready for emergency use.

Pharmaceutical firms have recently placed on the market injectable penicillin maintaining high blood level concentrations lasting two weeks. Should sensitivity occur the constant presence of penicillin in the blood might cause repeated attacks of anaphylactic shock (although we have never seen it) and we do not suggest its use in allergic individuals. Penicillin-O-Potassium in tablet and by injection has been recommended for patients sensitive to penicillin G, but we feared to use it after experiencing near fatal shock reactions with penicillin G. Desensitization may be attempted if absolutely necessary, but we usually switch to a different antibiotic.

The following case reports will illustrate our experience.

CASE 1.—W. M. was a 56-year-old fruit and produce store worker. He called at the office July 31, 1947, complaining of severe attacks of bronchial asthma for one year, which began after a cold and rhinitis for several months. He had a past history of three attacks of pleurisy with effusion, the last attack thirty-three years previously. Otherwise he had been well.

While under our care he had an x-ray of the chest, electrocardiogram, complete blood count, complete blood chemistry, and all were within normal limits. He was tested for inhalants, foods, pollen, bacteria, house dust, and molds, and was positive to ragweed pollen, a number of inhalants, molds, bacteria, and house dust. Appropriate extracts and their dilutions were made and treatment started. Asthmatic attacks were kept under control. However, he was subject to acute colds which were complicated by purulent bronchitis and asthma. It was then necessary to give him injections of penicillin for eight days before he recovered from his asthmatic bronchitis. During the first winter, two courses of penicillin injections, consisting of 8 each, were given. He was perfectly well the following summer and during a Florida visit from December to March. When he returned he had a severe attack of bronchitis followed by asthma. Daily injections of penicillin were given for eight days, with improvement.

After this he was well for six weeks, then caught another cold and again penicillin injections were begun. This time, within two minutes after the second injection (the twenty-sixth of the sum total of penicillin injections received), he was seized with a terrific anaphylactic shock. It was with difficulty that he was placed on the table with head and chest raised. He felt a burning sensation in his face and hands; the palms of hands, face, and neck turned red. He complained of terrific pains in his chest and over the precordium, and had a weak, imperceptible pulse. He pleaded for help in his extreme distress of wheezing, coughing, and orthopnea. Immediately 2 minims (0.12 ml.) of epinephrine (1:1,000) were administered intradermally and repeated every two minutes for four doses before he began to show signs of relief. The acute anaphylactic shock lasted twenty minutes.

He and his family were informed of his sensitivity to penicillin and advised never to have any further injections. Since then he has improved with desensitization treatment. Colds and asthma attacks are much less frequent and are controlled with aureomycin and other measures.

CASE 2.—A. M., aged 59, was married thirty-three years, and had 3 children. He worked in a leather tannery; he called at the office in February, 1948, complaining of bronchial asthma for six years. This began in the winter of 1942 after frequent colds, worse in winter and somewhat better in summer.

For the last six winters he had suffered from frequent colds, which were followed by severe attacks of dyspnea, wheezing, coughing, and purulent expectoration, occasionally tinged with blood. There was bilateral nasal obstruction, sneezing, and rhinitis (watery discharge) in the morning.

Physical examination showed him to be very undernourished, with large inflamed tonsils, pharyngitis, marked emphysema, numerous moist and dry râles scattered throughout his chest. There was moderate anemia; otherwise the blood was normal. Urine was normal, also the electrocardiogram.

Intradermal tests with inhalants, foods, pollens, bacteria, house dust, and molds showed little or no reactions.

Frequent colds, lasting one to two weeks, with or without fever, brought on several recurring attacks of bronchial asthma. These recurring infections, four to five times a year, were best controlled by daily injections of penicillin for periods of seven to ten days.

The first winter under our care he had 30 injections of penicillin; the second winter, he had two courses of penicillin. During the sixth course, started four weeks after the last previous series, within two minutes of the fourth injection he had a severe anaphylactic shock. (This was the sixty-fourth injection of the sum total of the penicillin received.) Burning and itching sensations occurred over all the body; his face and hands turned red; his lips became blue; he suffered severe chest pains, most pronounced in the precordial area. Wheezing, dyspnea, and orthopnea were very marked, and the pulse was imperceptible.

Injections of epinephrine (1:1,000), 2 minims (0.12 ml.) were immediately started, and repeated every two minutes. In all he had 10 minims (0.6 ml.) of epinephrine (1:1,000). It was twenty-four minutes before he quieted down. He was told his reaction was due to penicillin and he should never have any more. He insisted upon being given aonther trial injection because he felt convinced penicillin was a great factor in his recovery every time he had respiratory infection. One week later he received 30,000 units. Instantly he suffered the same type of anaphylactic shock experienced one week before. He was finally convinced of the danger of further injections of penicillin. Since then we have used aureomycin or other antibiotics to combat his upper respiratory infection.

CASE 3.—I. M., a white, single man, aged 49 years, a newspaper reporter for twenty years, called at the office in June, 1946, complaining of bronchial asthma and bilateral persistent nasal obstruction of two years' duration. He had irregular uncontrollable attacks of coughing, wheezing, dyspnea, and orthopnea. At times he had six or eight attacks of asthma in twenty-four hours. At other times he would be free from asthma for several weeks.

He was subject to colds in the spring (May) and the fall (October), but worse in the winter months. The nasal obstruction did not respond to any local treatment, to antihistaminics, or to three electrocauterizations.

On physical examination, his chest revealed dry and moist râles and wheezing. The patient did not have any knowledge of environmental contacts which might be in some way responsible for his respiratory difficulties.

We tested him with inhalants, foods, pollen, dust, molds, and antigens of bacteria responsible for upper respiratory infections. He did not show any typical immediate allergic skin reactions but delayed inflammatory local reactions to bacterial proteins and house dust. Clinically he was highly sensitive to insecticides, printer's ink, glue, and sizing material.

He had electrocauterization of his nasal turbinates in 1946 and 1947 by a nose and throat specialist. This was followed in 1950 by sclerosing (Silnosal) treatment of the turbinates with no improvement. In October, 1951, he had a polypectomy. Several months later he had another sclerosing treatment of the turbinates.

Courses of daily injections of penicillin (300,000 units) were given. After 6 or 8 injections he would make a satisfactory recovery and remain well from two to four weeks.

In April, 1951, he had a recurrence of his respiratory infection. Eight weeks had elapsed since the previous series of penicillin injections. Another course of penicillin, the seventh to date, was begun. After the third injection, which was approximately the fifty-fourth penicillin injection, he sustained a severe anaphylactic shock. It was difficult to place him on the table. He had itching all over the body, the face and hands turned red, lips blue. He was weak, with an imperceptible pulse, severe chest and precordial pains, dyspnea, and orthopnea. Intradermal injections of 2 minims (0.12 ml.) of epinephrine (1:1,000) were started immediately, and given every two minutes. In all, he had 10 minims (0.6 ml.) of epinephrine. It was twenty-four minutes before he recovered from shock. Since then we have used other antibiotics to combat his respiratory infections. The importance of avoiding all contact with fresh newspapers, magazines, and other lithographic material was explained to him. He was compelled to give up his reporter's position. He managed to obtain other employment as a secretary and public relations manager in a private fraternal organization. Since this change, for the last year and a half, he made almost a complete recovery.

SUMMARY

Although anaphylactic shock following penicillin injections in bronchial asthmatics is not common, we must be alert for it because of its severity when it does occur. Signs and symptoms that can forewarn of shock reactions have been discussed, emergency treatment outlined, and three illustrative cases presented.

REFERENCES

1. Goldman, Jack S.: Penicillin Reactions, Memphis M. J. **26**: 100, 1951.
2. O'Donovan, W. J., and Klorfajn, I.: Sensitivity to Penicillin, Lancet **2**: 444, 1946.
3. Sterling, Alexander, Fishman, Aaron E., and Sharps, Frank: Massive Dose of Penicillin in Chronic Asthmatics, Am. Pract. **2**: 570, 1948.
4. Sterling, Alexander: The Importance of Pre-Operative Local Treatment in Nose and Throat Surgery, Arch. Pediat. **65**: 377-380, 1948.
5. Thomson, W. O.: Sudden Death Following an Injection of Penicillin, Brit. M. J. **2**: 70, 1952.
6. Waldbott, George L.: Anaphylactic Death From Penicillin, J. A. M. A. **139**: 526, 1949.
7. Higgins, George A., and Rothchild, Thomas P. E.: Fatal Anaphylactic Shock From Procaine Penicillin, New England J. Med. **247**: 644, 1952.
8. Pratt-Thomas, H. R., and Waring, J. I.: Fatal Delayed Anaphylactic Shock After Penicillin, J. A. M. A. **131**: 1384, 1946.
9. Burleson, R. J.: Anaphylactoid Shock Due to Penicillin, J. A. M. A. **142** 562, 1950.
10. Everett, Reginald: Anaphylactic Reactions From Local Use of Penicillin, J. A. M. A. **146**: 1314, 1951.
11. Sterling, Alexander: Dangers Attending the Clinical Use of Epinephrine in Bronchial Asthma, M. Clin. North America **24**: 1851, 1940.

1737 CHESTNUT.

THE USE OF I^{131} IN IMMUNOLOGIC INVESTIGATION*

FRANK J. DIXON, M.D., PITTSBURGH, PA.

LABELING proteins with radioactive iodine, I^{131}, is a relatively simple technique and affords a most useful tool for immunologic investigation. Antibodies and protein antigens can be so labeled and subsequently traced in vivo or in vitro by virtue of their radioactivity. Typical experiments in which this tracer technique has been valuable are given at the end of this article.

Iodination of Proteins.—At a neutral or alkaline pH free iodine will combine with most proteins, principally in the tyrosine ring as shown in Fig. 1. The optimal pH for iodination varies with different proteins; for example, serum globulins, pH 7-8, serum albumins, pH 8-9, and ovalbumin, pH 9-10. The iodination procedure used in our laboratory is described by Talmage and associates.[1] In this procedure an aqueous solution of I^{131}, in the form of free iodine, is added to the protein solution buffered to the proper pH. An amount of nonradioactive carrier iodine calculated to supply a label of one iodine atom per molecule of protein is added to the I^{131}. Approximately one-third of the iodine will combine with most proteins under these conditions. The nonprotein bound I^{131}, in the form of iodide, may be separated from the I^{131} protein by dialysis or by ion exchange resin.[2] The entire reaction is carried out at 0° to 5° C. A wide range of concentrations of protein solutions may be employed, from 100 mg./c.c. to less than 1 mg./c.c.

Proteins lightly labeled with iodine as described above are immunologically and physiologically indistinguishable from native proteins.[3a, b, c, d] In addition, the I^{131} protein is an extremely stable compound. In vitro and in vivo studies indicate that the I^{131} remains attached to the protein until the latter is degraded beyond the point of immunologic recognition.[4a, b]

Methods of I^{131} Protein Measurement.—Once labeled, the proteins can be followed in test tube reactions or in animals by fairly simple quantitative measurements of the beta or gamma emissions from the I^{131}. For beta determinations, relatively small fluid or solid samples are dried in planchets and counted by thin end window Geiger tubes. Small amounts of material must be used in order to avoid absorption of the beta particles within the sample itself. Gamma determinations can be made using much more material since significant self-absorption of the penetrating gamma rays within the sample does not occur. Well-type scintillation crystals or Geiger tubes are

From the Department of Pathology, University of Pittsburgh School of Medicine.

Presented at the Postgraduate Course of the American Academy of Allergy, Feb. 15, 1952, Chicago, Ill.

Received for publication July 2, 1953.

*This study was supported by Atomic Energy Commission contract No. AT(30-1)-1205. This is reprint No. 25 of the Pathology Department, University of Pittsburgh School of Medicine.

particularly useful for gamma counting because tissue or fluid can be counted without drying or treating and later the same material can be used for chemical or immunologic studies.

When using I^{131}-labeled proteins in in vivo experiments, two simple precautions should be taken to insure that the I^{131} measured really represents the originally labeled protein. First, the host must be prevented from utilizing the I^{131} liberated by labeled protein catabolism in the synthesis of its own body constituents. Daily feeding of a small iodide supplement to experimental subjects during the period of observation will effectively reduce the utilization of this liberated I^{131} and insure its elimination, principally by the kidneys. Second, in tracing the labeled protein, measurement of I^{131} should represent only protein bound radioactivity, as indicated by trichloracetic acid precipitation. This prevents the presence of nonprotein bound I^{131}, liberated by labeled protein catabolism, from interfering with a true measure of the labeled protein. By measuring the nonprotein bound I^{131} excreted in the urine and remaining in the host, the rate of labeled protein catabolism can be calculated.

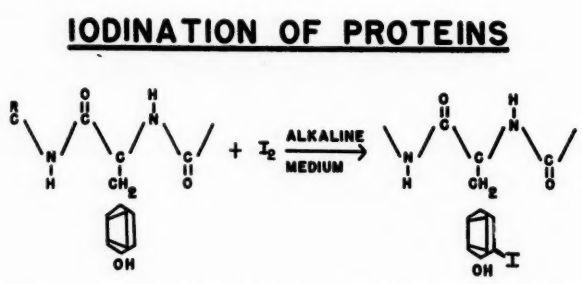

Fig. 1.—Diagrammatic representation of the principal site of combination of iodine and proteins.

In addition to the quantitative determinations of I^{131} by counters, an approximate histologic localization of I^{131} can be made by autoradiographs. In this technique, tissue from an animal receiving labeled protein is fixed in ordinary fixatives, embedded in paraffin, and sectioned according to usual histologic techniques. Then the sections are mounted in the dark on any of a variety of specially designed photographic emulsions and allowed to remain in the dark in contact with the emulsion for an appropriate exposure period, usually a matter of days, which will vary inversely with the amount of radioactivity in the section. After exposure, the photographic emulsion with tissue still attached is developed and then the tissue is stained with hematoxylin or some other suitable dye. The resultant preparation has the stained tissue section superimposed upon a photograph of its radioactivity composed of reduced silver particles in the emulsion immediately beneath the I^{131} in the tissue. Fig. 2 is a high-power photomicrograph of such a preparation made from the lung of a rabbit injected intravenously with I^{131} tagged azo dye labeled bovine gamma globulin. The I^{131} azo protein has been taken up by phagocytes in the alveolar walls and is identified by the dense foci of reduced black silver particles. Because the I^{131} emanations will penetrate many

microns through the photographic emulsion, the definition achieved by this method will not allow localization of the I^{131} to single cells. However, localization to larger histologic structures such as lymph follicles, small arteries, and veins, or bronchial walls, is easily achieved. For further information on autoradiographic techniques see references 5a and b.

These isotope techniques are not expensive: the special equipment needed for adequate handling and measurement of I^{131} costs approximately $2,000 and is available from a number of excellent firms. This equipment should include a thin mica end window Geiger tube for beta counting, a well-type Geiger tube or scintillation crystal for gamma counting, appropriate lead shields for the above tubes, a scaler to record the impulses picked up by these tubes, and 10 to 15 lead bricks for shielding during iodination of proteins. The techniques for handling I^{131} in the amounts needed for most immunologic studies are not difficult and could be learned in most competent isotope laboratories. If no such laboratory is available locally, an excellent four-week course on radioisotope techniques is offered several times each year by the Oak Ridge Institute for Nuclear Studies, Oak Ridge, Tenn.

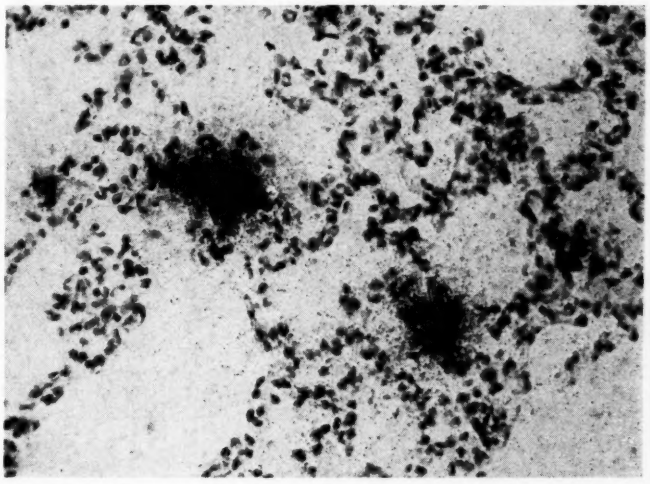

Fig. 2.—Autoradiograph of lung seen at high power. Two focal concentrations of black silver particles indicate localization of I^{131} protein in the alveolar walls.

Experimental Applications.—I^{131}-labeled protein antigens have been used by Drs. D. W. Talmage* and P. H. Maurer of our laboratory in the development of an extremely useful quantitative precipitin test.[6] This test measures the antigen-precipitating capacity of an antiserum and is, therefore, a measure of the function rather than the weight of antibody. The greatest advantage of this procedure is that quantitative precipitin determinations can be made on as little as 1 or 2 ml. of weak antiserum. This makes it possible to do frequent repeated antibody determinations on an animal without subjecting

*Present address, Department of Medicine, University of Chicago, Chicago 37, Ill.

it to the large unphysiologic bleedings necessary to obtain enough serum for the conventional quantitative precipitin nitrogen determinations.

This test is carried out as follows: to ½ ml. of antiserum an amount of I^{131} antigen is added which will give a slight antigen excess. Then the usual quantitative precipitation procedure is followed. After precipitation is completed the supernate is decanted and the precipitate washed. Radioactivity determinations of I^{131} antigen in the precipitate and in the supernate plus washings are made. From two or more such determinations in the region of antigen excess the antibody precipitating capacity of an antiserum can be calculated. We express this capacity arbitrarily as the amount of antigen precipitated by 1 ml. of antiserum at the point of 80 per cent antigen precipitation.

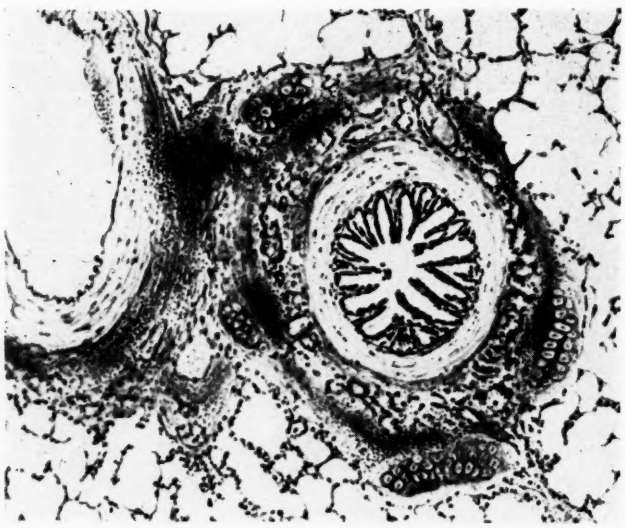

Fig. 3.—Autoradiograph of lung from guinea pig dying in anaphylactic shock induced by an I^{131} protein antigen. Note granular silver deposition in bronchial wall between muscle and cartilage and between bronchus and pulmonary artery indicating concentration of I^{131} antigen.

I^{131} proteins have had numerous in vivo experimental applications. Since the I^{131} label is not separated from the protein until the latter is catabolized beyond the point of immunologic recognition, and since the I^{131} liberated by catabolism of the labeled protein is almost entirely excreted in the urine, this technique is extremely useful for measuring rates of protein degradation. Determination of the half-lives of homologous gamma globulin or antibody in several species including man was made by following the plasma levels of passively administered I^{131}-labeled homologous gamma globulin.[7] The rate of disappearance of I^{131} protein from the plasma was considered to be the rate of protein degradation. The gamma globulin half-lives of thirteen days in adult human beings, twenty days in children, twenty-one days in cows, eight days in dogs, five days in rabbits, and one to two days in mice determined by this method are very similar to immunologically determined half-lives of

passively administered homologous antibody. As might be expected, the gamma globulin half-lives vary inversely with the metabolic rates of the different species expressed per unit weight.

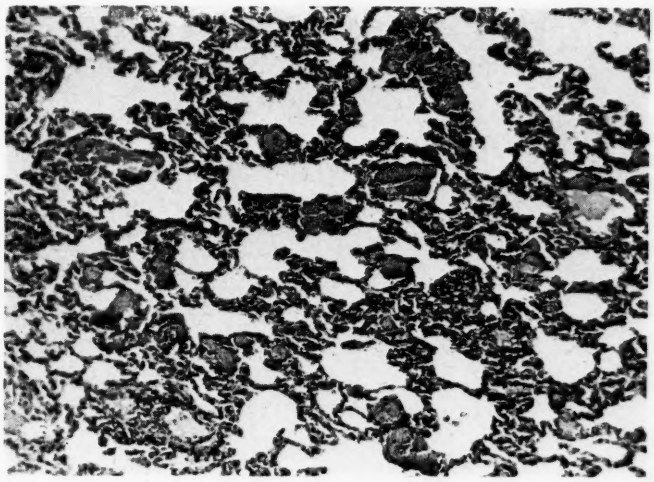

Fig. 4.—Ordinary microscopic section of the lung of a rabbit dying in anaphylactic shock induced by an I^{131} protein antigen. Note the large homogeneous masses distending many of the pulmonary capillaries.

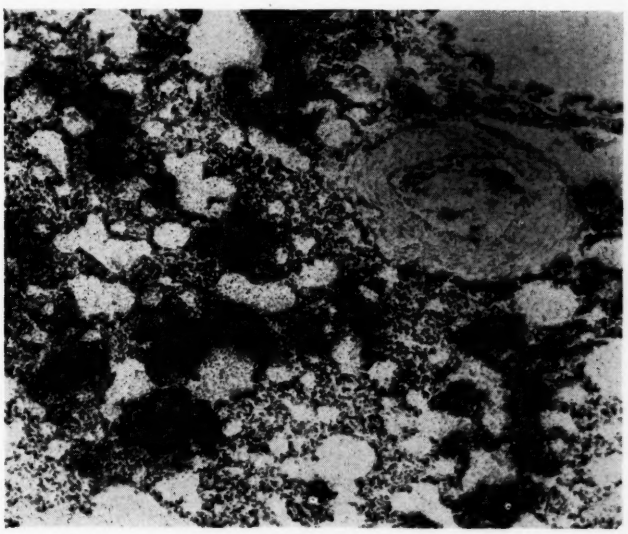

Fig. 5.—Autoradiograph prepared with section adjacent to that seen in Fig. 4. The dark concentrations of reduced silver particles indicating I^{131} protein antigen correspond to the homogeneous masses occluding pulmonary capillaries seen in Fig. 4.

Several studies have utilized the I^{131} label in tracing protein antigens. One of the earliest of these was the tracing of antigen in anaphylactic shock in guinea pigs.[8a, b] A shocking dose of I^{131}-labeled antigen was given intravenously to previously sensitized pigs. Following the anaphylactic shock, various tissues of the pigs were analyzed for radioactivity. Considerable

antigen was found in the lungs, principally in regions of peribronchial vascular dilatation and edema which developed during the brief period of shock. This localization of antigen was easily demonstrated by autoradiograph as illustrated in Fig. 3.

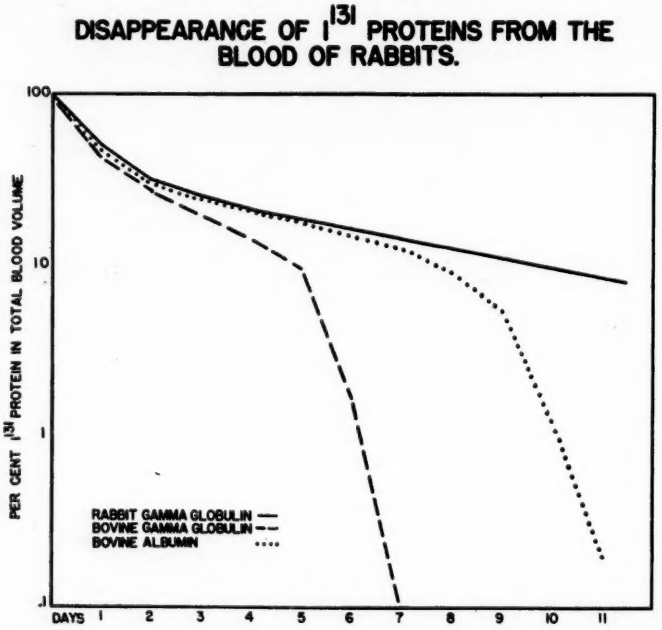
DISAPPEARANCE OF I131 PROTEINS FROM THE BLOOD OF RABBITS.
PER CENT I131 PROTEIN IN TOTAL BLOOD VOLUME
100
10
1
.1
DAYS 1 2 3 4 5 6 7 8 9 10 11
RABBIT GAMMA GLOBULIN
BOVINE GAMMA GLOBULIN
BOVINE ALBUMIN

Fig. 6.—Semi log plot of the percentage of the original injection of I^{131} protein found in the total blood volume following intravenous injection. Equilibration of I^{131} protein between intravascular and extravascular components of the plasma protein pool results in a drop in blood concentration of about 50 per cent within the first one to two days. Homologous and heterologous proteins are catabolized at comparable rates until antibody to the latter appears. Antibody to bovine gamma globulin increases rate of antigen elimination by the fourth day after antigen injection, and antibody to bovine albumin by the eighth day.

Antigen tracer studies in anaphylactic shock in rabbits also showed localization of I^{131} antigen in the lungs. In this instance, however, the radioactive antigen was found incorporated in eosinophilic acellular masses that completely occluded small capillaries in the alveolar walls. Fig. 4 shows an ordinary microscopic section of the pulmonary parenchyma of a rabbit fatally shocked with I^{131} antigen. Fig. 5 is from an adjacent section prepared as an autoradiograph. The black silver deposits indicating radioactivity in the autoradiograph correspond to the structureless plugs occluding the alveolar capillaries in Fig. 4. It seems likely that these masses filling the alveolar capillaries are intravascular I^{131} antigen-antibody precipitates which form after intravenous injection of the antigen into an animal with considerable circulating antibody. The extent to which this capillary occlusion contributes to the pulmonary vascular obstruction of rabbits in anaphylaxis is difficult to determine, but it is possible that it might play a considerable role.

The fate of heterologous serum protein antigens after first injection into rabbits has also been studied using I^{131}-labeled antigens.[9] In this instance the

tracing of a labeled antigen makes possible an early measure of the immune response as indicated by the rate of antigen catabolism or elimination.[1] As shown in Fig. 6, within the first twenty-four to forty-eight hours after injection, heterologous serum protein antigens equilibrate within the plasma protein pool of the host just as do homologous proteins, resulting in a drop in serum antigen concentration to 50 per cent of the immediate postinjection level. After this equilibration, the antigen disappears at a relatively slow, logarithmic rate until antibody becomes available. This period of nonimmune antigen catabolism lasts for approximately four days in the case of bovine gamma globulin and for eight days with bovine serum albumin. The availability of antibody is reflected in a rapid or immune antigen elimination rate beginning at four days for bovine gamma globulin and eight days for bovine serum albumin, several days before immunologically detectable free antibody is present in the serum.

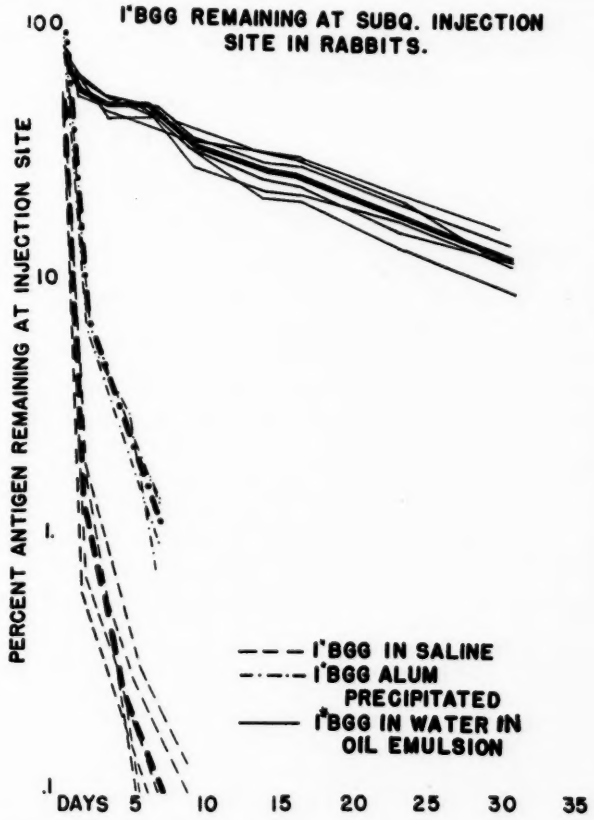

Fig. 7.—Semi log plot of the elimination of I^{131} protein antigen from local intramuscular injection site. The I^{131} antigen in water in oil emulsion was retained for a much longer time at the injection site than was the alum-precipitated I^{131} antigen.

Attempts to trace the I^{131}-labeled heterologous serum protein antigens in the tissues after a single injection into rabbits have yielded results at variance with those obtained tracing particulate antigens,[10] polysaccharide

antigens,[11a, b, c] and dye labeled or heavily iodinated protein antigens,[12a, b, c, d] all of which are partially retained in the tissues, principally in the reticulo-endothelial system. The trace labeled I^{131} protein antigens are not retained in the tissues in significant amounts but rather appear to be readily catabolized by the host.[9]

The ability of adjuvants to hold antigens at the local injection site has also been measured with the use of I^{131}-labeled antigens.[13] In this study the antigen, I^{131} bovine gamma globulin, was prepared in three forms: in Freund adjuvant (water in oil emulsion), as an alum precipitate, and in soluble form in a saline solution. Identical volumes (1 c.c.) of each of these three preparations were injected subcutaneously into rabbits. The rates of elimination of the three forms of antigen from the injection sites were determined by repeated external measurement of the gamma radiation. The injections were made into the leg and the measurement of antigen at the injection site was accomplished by placing the injected leg into a well-type gamma counter and determining the amount of residual radioactivity. Comparison of the rates of antigen dissemination is made in Fig. 7. The water in oil emulsion was quite effective in holding antigen while the antigen in the alum-precipitated preparation was disseminated rapidly.

These are a few of the applications of the I^{131} tracer techniques which have been employed in our laboratories. Numerous other studies utilizing the same basic techniques have been undertaken elsewhere; a review of these is beyond the scope of this presentation. It is apparent that the most important application of this experimental approach is in the investigation of the dynamic in vivo aspects of immune reactions where sites of reaction and rates of degradation and elimination of antigens and antibodies are important. During the past five or six years the observations which have been made possible by this technique have established it as one of the valuable tools in the immunologist's armamentarium.

REFERENCES

1. Talmage, D. W., Dixon, F. J., Bukantz, S. C., and Dammin, G. J.: Antigen Elimination From the Blood as an Early Manifestation of the Immune Response, J. Immunol. **67**: 243, 1951.
2. Lutwak, L.: Preparation of Radioactive Iodinated Serum Albumin, Proc. Soc. Exper. Biol. & Med. **80**: 741, 1952.
3a. Eisen, H. N., and Keston, A. S.: The Immunologic Reactivity of Bovine Serum Albumin Labelled With Trace-Amounts of Radioactive Iodine (I^{131}), J. Immunol. **63**: 71, 1949.
b. Banks, T. E., Francis, G. E., Mulligan, W., and Wormall, A.: The Precipitin Reaction and Antibody Valence Studied With the Aid of Radioactive Isotopes, Nature **165**: 111, 1950.
c. Pressman, D., and Sternberger, L. A.: The Relative Rates of Iodination of Serum Complement and Effect of Iodination on Antibody Activity, J. Am. Chem. Soc. **72**: 2226, 1950.
d. Masouredis, S. P., Melcher, L. R., and Koblick, D. C.: Specificity of Radio-iodinated (I^{131}) Immune Globulin as Determined by Quantitative Precipitin Reactions, J. Immunol. **66**: 297, 1951.
4a. Knox, W. C., and Endicott, F. C.: I^{131} as an Antigen Label in the Circulating Serum of Non-immune Rabbits, J. Immunol. **65**: 523, 1950.
b. Melcher, L. R., and Masouredis, S. P.: The In Vivo Stability of the I^{131} Protein Label of Rabbit Antibody in Guinea Pigs as Determined by the Quantitative Precipitin Reaction, J. Immunol. **67**: 393, 1951.

5a. Fitzgerald, P. J.: Radioautography in Cancer, Cancer **5**: 166, 1952.
b. Fitzgerald, P. J., Semmel, E., Weinstein, J., and Martin, C.: Radioautography: Theory, Technic and Applications, Lab. Invest. **2**: 181, 1953.
6. Talmage, D. W., and Maurer, P. H.: I^{131} Labelled Antigen Precipitation as a Measure of Quantity and Quality of Antibody, J. Infect. Dis. **92**: 288, 1953.
7. Dixon, F. J., Talmage, D. W., Maurer, P. H., and Deichmiller, M. P.: The Half-life of Homologous Gamma Globulin (Antibody) in Several Species, J. Exper. Med. **96**: 313, 1952.
8a. Warren, S., and Dixon, F. J.: Antigen Tracer Studies and Histologic Observations in Anaphylactic Shock in the Guinea Pig. Part I, Am. J. M. Sc. **216**: 136, 1948.
b. Dixon, F. J., and Warren, S.: Antigen Tracer Studies and Histologic Observations in Anaphylactic Shock in the Guinea Pig, Part II, Am. J. M. Sc. **219**: 414, 1950.
9. Dixon, F. J., Bukantz, S. C., Dammin, G. J., and Talmage, D. W.: The Nature and Significance of the Antibody Response. Symposium, New York, 1953, Columbia University Press, p. 170.
10. Wilson, G. S., and Miles, A. A.: Principles of Bacteriology and Immunity, ed. 3, Baltimore, 1946, Williams & Wilkins Company, vol. 2, p. 1034.
11a. Felton, L. D.: The Significance of Antigen in Animal Tissue, J. Immunol. **61**: 107, 1949.
b. Kaplan, M. H., Coons, A. H., and Deane, H. W.: Localization of Antigen in Tissue Cells. III, J. Exper. Med. **91**: 15, 1949.
c. Alan, G. S., Hill, M. B., Deane, H. W., and Coons, A. H.: Localization of Antigen in Tissue Cells. V, J. Exper. Med. **92**: 35, 1950.
12a. Sabin, F. R.: Cellular Reactions to a Dye Protein With a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**: 67, 1939.
b. Kruse, H., and McMaster, P. D.: The Distribution and Storage of Blue Antigenic Azo Proteins in the Tissues of Mice, J. Exper. Med. **90**: 425, 1949.
c. McMaster, P. D., and Kruse, H.: The Persistence in Mice of Certain Foreign Proteins and Azo Protein Tracer-Antigens Derived From Them, J. Exper. Med. **94**: 323, 1951.
d. Haurowitz, F., and Crampton, C. F.: The Fate of Intravenously Injected I^{131} Iodo Ovalbumin, J. Immunol. **68**: 73, 1952.
13. Talmage, D. W., and Dixon, F. J.: The Influence of Adjuvants on the Elimination of Soluble Protein Antigens and the Associated Antibody Responses, J. Infect. Dis. (in press).

Editorial

SHOULD ONE USE ACTH AND ADRENAL CORTICOSTEROIDS IN SEASONAL ALLERGIES?

THE question whether corticotropin or adrenal corticosteroids should be used in seasonal allergies may seem unrealistic since the hormones are now used extensively, in the treatment of both seasonal and perennial allergic conditions. However, a review of the complications produced by the administration of either hormone in a large number of patients makes us feel that the rationale of the fashionable endocrine approach to problems of allergy should be re-examined in the light of recent experience.

Why corticotropin? Selye's concepts suggest that chronic illness might result from hormonal imbalance. The metabolic state of connective tissue is controlled by a balanced supply of "salt" and "sugar" hormones. If prolonged stress decreases production of either anterior pituitary hormone or compound F, the affected tissue may indicate the deficiency by the development of a secondary edema. Exogenous corticotropin restores the deficient glucocorticoid output to normal and corrects the pathologic behavior of the target organ.

Allergic diseases, however, are not diseases of adaptation. Tissue edema in allergy is primary, caused by antigen-antibody union in the shock organ, e.g., the respiratory tract or skin. The pituitary and adrenal function of allergic patients is normal. A normal supply of glucocorticoids is not sufficient to undo the profound alteration of the shock tissue. Levels above normal are needed for effective therapy.

Therapy with ACTH or adrenal corticosteroids is symptomatic therapy. Stress is not relieved by the hormones. The immunomechanism of the allergic reaction remains unaltered. Edema, secondary or primary, is suppressed while the hormones are given. Upon withdrawal of medication, the symptoms recur. In fact, they may recur with increased severity because the administration itself depresses the endogenous production of the hormones in their respective glands. As the result, the glands do not maintain even the pretreatment level of the hormones, so the patient may be worse off than at the beginning of therapy.

On the basis of the "thermostat" principle of glandular function, it becomes hazardous indeed to administer ACTH or adrenal corticosteroids to the allergic patients most in need of it—those with severe perennial allergic disease. In seasonal allergies, on the other hand, the edematous tissues will revert to normal at the end of the period of exposure to the specific antigen. The tissue demand for glucocorticoids will diminish, and a temporary hypofunction of anterior pituitary or adrenal cortex is not likely to cause alarming symptoms. Benefit during the peak of the ragweed season, particularly in instances of disabling bronchial asthma, is often so spectacular that one has good reason to resort to the hormones for the symptomatic management of those patients, and of only those patients, who fail to respond to more conservative measures.

The choice of corticotropin or adrenal corticosteroids for hormone therapy depends at present: (1) on one's inspired guess whether a hypofunction of the pituitary or of the adrenal cortex is the lesser of two evils, and (2) on the convenience of administration. Adrenal corticosteroids can be given by mouth; but the gel-form of purified corticotropin, injected with ease daily or every other day, has the decided advantage of keeping the patient under close medical supervision.

Supervision is imperative. The precautions which are recommended for the prolonged administration of corticotropin in life-threatening disease apply equally to transitory therapy. A series of injections, for instance, of corticotropin—80, 60, 40, and 20 units, each dose repeated on two consecutive days—demands observation of weight and blood pressure, low-salt (but not necessarily salt-free) diet, adequate supplies of potassium chloride (a minimum of 3 Gm. a day, in divided doses) and the understanding that even short courses of therapy may produce serious psychologic reactions in unstable individuals. The danger of masking of infections requires recognition of early signs of inflammation, such as reddening of the nasal mucous membrane or a slight cough, which might be treated lightly or disregarded in patients not receiving the hormones. It is unlikely that Cushing's syndrome will develop within one week of treatment, but rapid formation, and silent rupture, of peptic ulcers have occurred in ulcer-prone patients.

Every therapeutic measure, particularly the specific treatment of disease, carries a certain risk. At times, considerable risk may be justified by the expected benefits. Yet, of all therapeutic risks, those of symptomatic therapy must be lowest, as a rule, close to zero. The literature makes us suspect that many physicians are awed by the great potential of corticotropin and adrenal corticosteroids. If in our minds we clearly label the hormones as what, for our practical purposes, they are: symptomatic agents at a magnificent level, but not more than symptomatic agents, fewer risks would be taken, and the answer to the question of the title, still yes, could be given with less reluctance and with much more ease.

M. S.

American Academy of Allergy

Postgraduate Courses and Scientific Program

TENTH ANNUAL MEETING, SHAMROCK HOTEL, HOUSTON, TEXAS

FEB. 1, 2, AND 3, 1954

A. Postgraduate Courses in Allergy (Preliminary Program), Jan. 29-31, 1954

COURSE 1. SPECIAL SUBJECTS IN CLINICAL ALLERGY

Friday, Jan. 29, 1954

10:00 A.M.-12:00 Registration.

2:00 P.M.- 5:00 P.M. Visiting Allergy Clinic: Dr. Will Spain, Dr. Walter Burrage, Dr. Bram Rose, Dr. Theodore Squire, Dr. DeWitt Hotchkiss, Jr.
Presentation of patients representing various problems in diagnosis and therapy.

Saturday, Jan. 30, 1954

9:00 A.M.-11:00 A.M. Symposium on ACTH-Cortone Therapy in Allergic Diseases. Dr. Bram Rose and other discussants.

11:00 A.M.-12:30 P.M. Chronic Allergic (Vasomotor) Rhinitis Including Interrelationships of Sinusitis and Polyps. Dr. Walter L. Winkenwerder, Dr. Will Spain, Dr. Bram Rose, and Dr. DeWitt Hotchkiss, Jr.

2:00 P.M.-5:00 P.M. Dermatology: Symposium on Allergic Skin Diseases. Dr. Adolph Rostenberg and other discussants.

COURSE 2. SEMINARS

(Afternoon of January 30 and morning of January 31)

These seminars are designed to keep advanced students informed of developments in applied and investigative phases of allergy. The subjects to be discussed are:

1. Histamine metabolism: biochemistry, synthesis, release, degradation; assay by biological, chemical, and tracer methods; physiologic action in relation to allergic states. Conducted by E. A. Zeller, Professor of Biochemistry, Northwestern University, and others.

2. Formed Blood Elements. The function of the various formed blood elements and their alteration in the allergic states. Conducted by William Dameshek, Director of the Blood Research Laboratory, New England Center Hospital, Boston, and others.

3. Species Patterns of Hypersensitiveness in Animals: Its Application to Human Allergy. A summary of the extensive studies of hypersensitiveness in various mammalian species correlated with their physiologic behavior. Significance of the differences in the interpretation of allergy in human beings. Course to be given by Drs. Samter, Saul Malkiel, and others.

COURSE 3. ALLERGENIC MOLDS AND POLLENS; IDENTIFICATION, DISTRIBUTION, CLINICAL SIGNIFICANCE

(January 29, 30, and morning of January 31)

The instruction in pollen recognition and in the standard technique of pollen counting will be under the supervision of Oren C. Durham. The instruction in recognition of fungus spores and fungi on gravity slides and culture plates will be supervised by Dr. Clyde M. Christensen, Professor of Mycology, University of Minnesota, and other well-qualified instructors.

The course, which will run concurrently with the preconvention clinical courses and seminars, is designed for technicians and physicians.

Fees:	Courses 1 and 2 combined	$50
	Course 2	15
	Course 3	35

Please send applications indicating course or courses selected to: Mr. A. Luthmers, American Academy of Allergy, 208 E. Wisconsin Ave., Milwaukee, Wis.

Checks should be made payable to the American Academy of Allergy.

B. Scientific Program (Preliminary), Feb. 1-3, 1954

MONDAY, FEBRUARY 1

Paper No.

1. A Study of Timed Vital Capacity and Forced Respiratory Curves in Patients With Pulmonary Disease. H. Beecher Chapin, Jean Roy, and Robert A. Cooke, New York, N. Y.
2. Clinical and Laboratory Estimation of the Severity of Bronchial Asthma. Francis C. Lowell, Irving W. Schiller, and Mary T. Lynch, Boston, Mass.
3. The Effect of Helium-Oxygen Mixtures on Pulmonary Function in Asthmatic and Emphysematous Patients. Irving W. Schiller, Francis C. Lowell, Mary T. Lynch, and William Franklin, Boston, Mass.
4. Maintenance Cortisone in Intractable Asthma: Preliminary Observations of Undesirable Cortisone Effects. John W. Irwin, Philip H. Henneman, David M. K. Wang, and Walter S. Burrage, Boston, Mass.
5. Prolonged Cortisone and Hydrocortisone Therapy. Carl E. Arbesman and Norman B. Richard, Buffalo, N. Y.

Intermission

6. Comparative Results of the Use of Hydrocortone, Cortisone, and ACTH in the Treatment of Intractable Bronchial Asthma and Pulmonary Emphysema. H. A. Bickerman and Alvan L. Barach, New York, N. Y.
7. The Use of Continuous Cortone Therapy in Elderly Asthmatics. Walter L. Winkenwerder, Baltimore, Md.
8. ACTH and Cortisone in the Treatment of Bronchial Asthma. Horace S. Baldwin, Paul F. de Gara, Aaron D. Spielman, and Murray Dworetzky, New York, N. Y.
9. The Excretion of Adrenocortical Steroids in Cases of Allergy. Bram Rose and E. H. Venning, Montreal, Canada.

Lunch

Guest Lecturer

2:00-3:00

The Development of Immunohematologic Concepts. William Dameshek, Director of the Blood Research Laboratory, New England Center Hospital, Boston, Mass.

Intermission

10. Effects of Histamine and Epinephrine on the Small Pulmonary Blood Vessels of Living Rabbits: An Experimental Study [Color Film]. Walter S. Burrage, John W. Irwin, and James I. Gallemore, Boston, Mass.
11. The Role of Adrenalin and a Monoamine Oxidase Inhibitor (Marsilid) in Anaphylaxis. Joseph Rebhun and Samuel M. Feinberg, Chicago, Ill.

12. Effect of Antitubercular Drugs on the Metabolism of Histamine and Sympathomimetic Amines. J. Barsky, E. R. Berman, J. R. Foute, and E. Albert Zeller, Chicago, Ill.

13. Release of Histamine in the Blood of Ragweed Sensitive Individuals. Joseph W. Noah and Alta Brand, St. Louis, Mo.

14. Comparison and Analysis of Lewis' Triple Response in Man Produced by (1) Histamine Phosphate and (2) a Histamine Liberator (Compound 48-80). Norman J. Ehrlich, Ruth Rhines, and Max Samter, Chicago, Ill.

TUESDAY, FEBRUARY 2

15. The Antigenic Relationship of the Pollen, Seed, and Leaves of Giant Ragweed. Samuel M. Feinberg, Joseph Rebhun, and Saul Malkiel, Chicago, Ill.

16. Studies on the Effect of Increasing the Concentration of Extraction on Yields of Allergenic Activity and Nitrogen Content. I. Timothy and Ragweed Pollen. Stanley F. Hampton, Mary C. Johnson, Sam Frankel, and Aline Schiele, St. Louis, Mo.

17. Chemical and Paper Chromatographic Investigation of Ragweed Pollen Extract. Sam Frankel, Mary C. Johnson, Aline Schiele, Samuel C. Bukantz, and Harry L. Alexander, St. Louis, Mo.

18. The Separation of Labeled Ragweed Antigen and Antiragweed Antibody. David W. Talmage, Chicago, Ill.

19. Complement Fixation Studies in Ragweed Allergy. Joseph Portnoy and William B. Sherman, New York, N. Y.

20. Immunochemical Studies of House Dust Allergen. Dan H. Campbell, Donald Z. Silver, and Wilton Vannier, Pasadena, Calif.

Intermission

21. Bronchial Asthma Unrelated to Positive Skin Reactions. Hyman Miller and Dorothy W. Baruch, Beverly Hills, Calif.

22. Skin Test Responses to Insulin and Serum Antihormonal Activity in a Case of Combined Insulin Allergy and Resistance. Samuel C. Bukantz and William G. Klingberg, St. Louis, Mo.

11:30 A.M. Dr. Murray Peshkin. Address by President, American College of Allergy.

Presidential Luncheon

President's Address. Ben Z. Rappaport

Guest Lecturer

2:00-3:00

The Dynamics of the Immune Response. Frank J. Dixon, Professor of Pathology, University of Pittsburgh, School of Medicine, Pittsburgh, Pa.

Intermission

23. Sensitivity to Digitalis (A Case Report). Milton M. Mosko, Chicago, Ill.

24. Passive Cellular Transfer of Neoarsphenamine Hypersensitivity in Guinea Pigs. A Oliveira Lima, Rio de Janeiro, Brazil.

25. Allergy to Foods Containing Sulfur-Amino-Acids; Case Report and Clinical Study. Louis Tuft, L. N. Ettelson, and Herbert Schwartz, Philadelphia. Pa.

26. Allergy and Immunization for Wasp Stings. Mary Hewitt Loveless, New York, N. Y.

Annual Business Meeting, 4:30 P.M.

WEDNESDAY, FEBRUARY 3

27. House Dust Allergy: I. Occurrence and Incidence of Seasonal Patterns of Asthma and Rhinitis. A. M. Targow, Los Angeles, Calif.
28. Further Studies on Biological Properties of Staphylococcus Extract. Murray Dworetzky, Horace S. Baldwin, Morton C. Kahn, and Marilyn K. Smart, New York, N. Y.
29. Haptene Aerosol Desensitization of Guinea Pigs Passively Sensitized to Specific Pneumococcus Polysaccharides. Oscar Swineford, Jr., Charlottesville, Va.
30. Studies on the Secondary Sensitization of Animals During Aerosol Induced Anaphylactic Shock in the Analysis of the Pathogenesis of Sensitization. Max Samter, Z. Z. Godlowski, and B. Z. Rappaport, Chicago, Ill.

Intermission

31. Tissue Cultures in Immunologic Studies of Hodgkin's Disease. Jack M. Rose and Jack R. Pulliam, Houston, Texas.
32. Allergic Dermatitis to Asparagus; A Case Presentation. Walter R. Kessler and James H. Barnard, New York, N. Y.
33. Topical Use of Hydrocortisone (Compound F) Ointment in Allergic Dermatoses. Sidney Friedlaender and Alex S. Friedlaender, Detroit, Mich.
34. Urticaria and Angioneurotic Edema: Statistical Survey of Five Hundred Cases. Milton J. Steinhardt, Detroit, Mich.

Book Reviews

La Pollinosi. By Umberto Serafini and (for the botanical section) Giuseppe Gola. Florence, Stab. Grafici A. Vallecchi, 1952, 430 pages. Price, 1600 lire.

American students and physicians desiring information on the various aspects of allergic conditions have a wide choice of good textbooks published in this country in a steady stream. In many foreign countries the situation is quite different and special works on this subject are few or are not available at all. The present volume, therefore, written by Dr. Serafini, a fellow of the American Academy of Allergy and an associate of Dr. C. Frugoni of the University of Rome, is a welcome addition to the foreign literature and should be gratefully received by our Italian colleagues.

Until recently pollinosis was considered rare and a rather benign condition in Italy. This concept has been revised by the author's extensive experimental and clinical studies which, together with a broad discussion of the research carried out by other workers, form the basis of this new and for Italy pioneering book. Pollinosis is defined as comprising all allergic manifestations of the different organs and apparatus produced by pollens in subjects possessing a specific hypersensitivity.

Following short chapters on terminology and history, G. Gola contributes a survey of the plants responsible for pollinosis in Italy. Tree pollens are hardly significant. There is a grass pollen season in the spring, and a summer-fall season due to the composite family and also to grasses, while in some parts of Italy, e.g., Sicily, *Parietaria officinalis* (wall pellitory according to the U. S. Dispensatory) is in bloom practically all year. The importance of Parietaria is stressed throughout the book. It is the leading hay fever plant in Italy and causes asthma in 67 per cent of its victims. A photograph of the pollen of this interesting plant should have been reproduced. Ragweed, on the other hand, is absent in Italy (as in all Europe). Insect-pollinated plants are given more credit for causing hay fever than is customary in this country. (Handling the flowers by man, e.g., for making perfumes, and loss of much of the pollens by the insects which carry them are among the reasons given.) Pollination calendars for the various sections of Italy are supplied, but it must be regretted that no figures of pollen counts are given.

Chapters on etiology, pathogenesis, pathological anatomy, symptomatology, diagnosis, complications, prognosis, prophylaxis, and therapy follow in this order and give a well-rounded picture of the problems concerned. The latest results in research and treatment with hormones are adequately presented. The author's judgment is generally sound and conforms to the principles and practices accepted in this country. In a detailed report on skin reactions in 1,343 patients, believed to be of clinical significance, 72 plant families and some 350 individual species of plants are listed, many of them insect-pollinated flowers.

Each chapter is followed by a bibliography containing numerous references which cover among others most of the important contributions of the American literature. A subject index and more numerous and better illustrations would increase the value of the book.

S. W. L.

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